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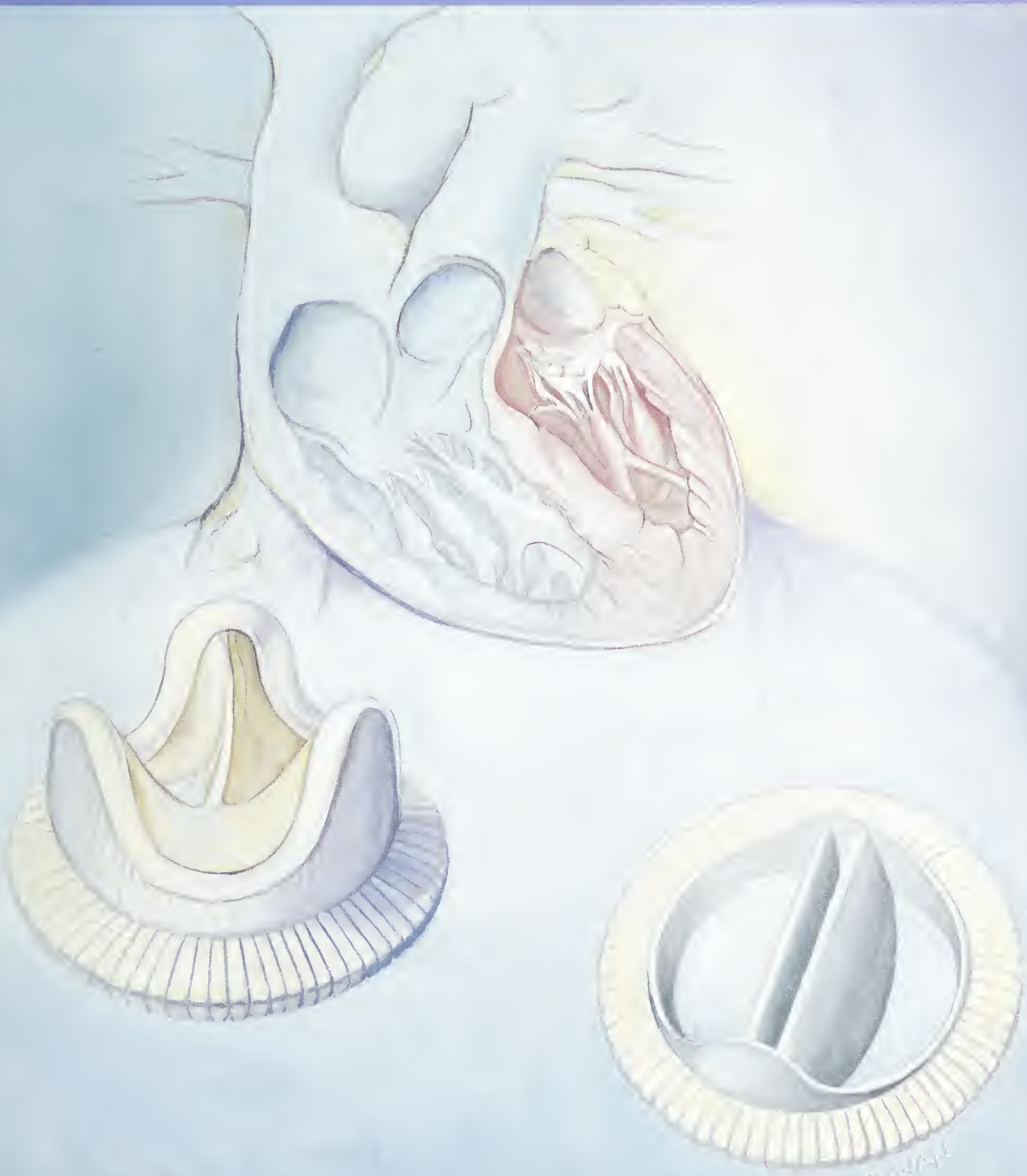

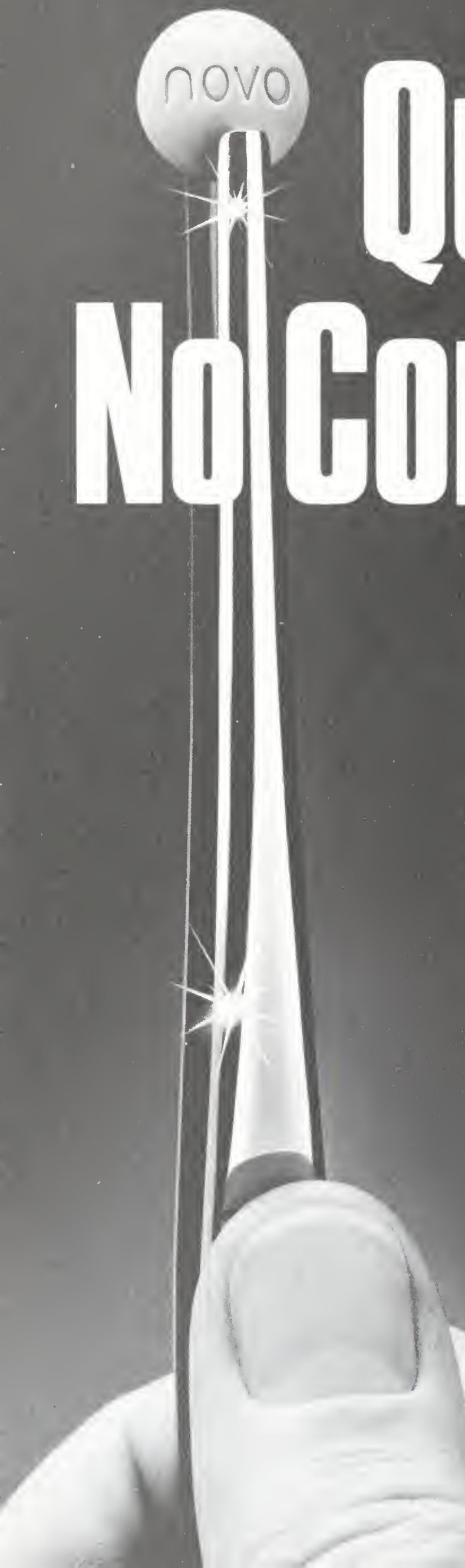

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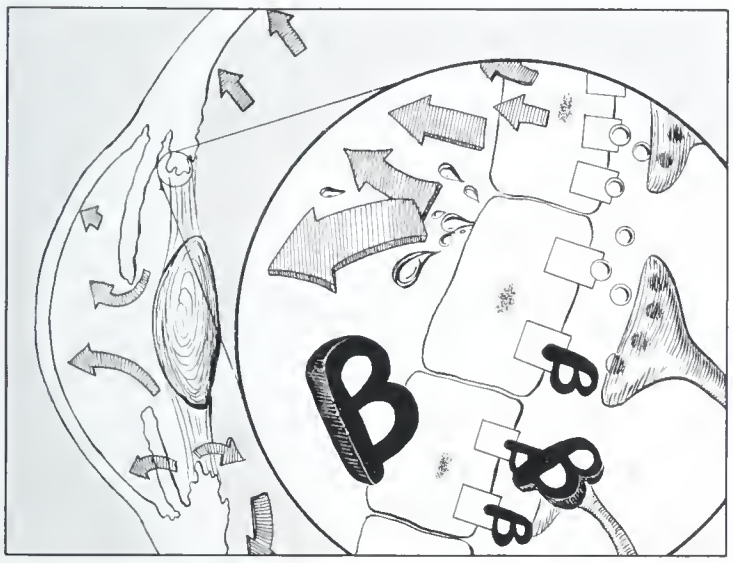

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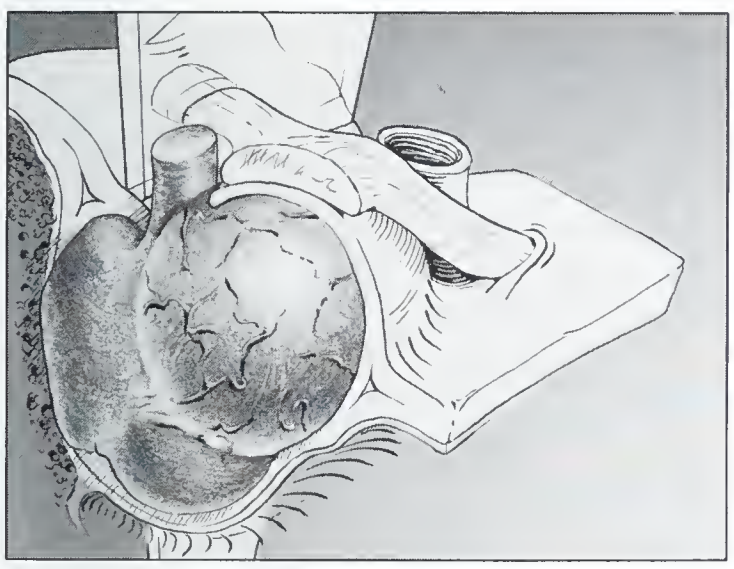

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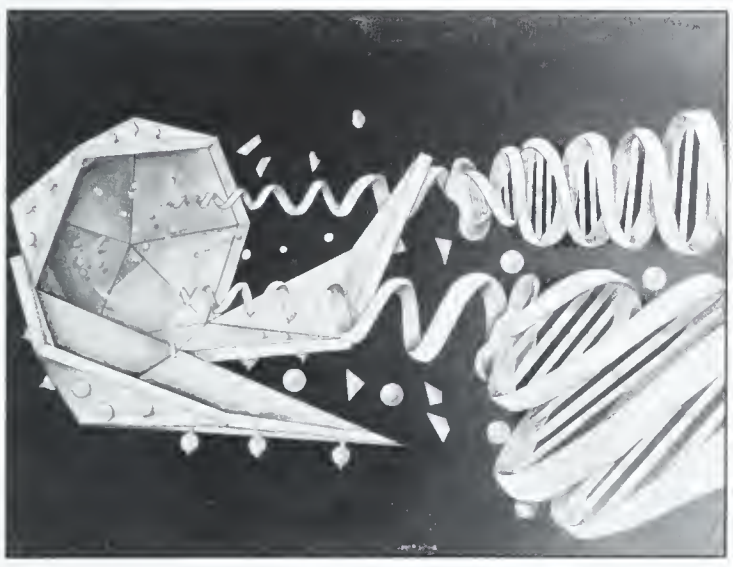

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Editorial

Founded in 1923, the University of Toronto Medical Journal is celebrating its 69th year of publication. As editors, we would like to thank the members of the editorial board and those authors who contributed to our first issue for their efforts.

As in previous issues, this edition of the UTMJ features the work of artists from the Department of Surgery's Division of Biomedical Communications. Illustrations from students in the BScBMC 9T3 and 9T4 programs accompany each article. A special thank-you to Elisabeth Rowan whose artwork on mitral valves graces our cover.

In this issue, Finkelstein et al discuss the use of beta-blockers in reducing intraocular pressure and examine its potential application to glaucoma treatment. In an excellent review, Rao and colleagues provide a look at mitral valve replacement through the years. This article will be of tremendous help to the student studying cardiology as well as to those with an interest in prosthetic valves and heart surgery.

In the first of two reviews, Yu and Young review vaccine strategies for HIV infection, while Grant and Poon review the medical and surgical management of prolactinomas. Other articles include a case report of intestinal volvulus presenting as acute pancreatitis from Ken Berger, an examination of the effects of ionizing radiation on the head and neck in tumorigenesis from Deitel et al., and a consideration of the therapeutic use of laughter in the pediatric population by Sheryl Nirenberg.

For those of you who were unable to attend the recent Gairdner Award lectures or who would just like to know more about the award recipients, Shabbir Alibhai profiles this past year's winners. In addition, Cheah and Flanagan present three challenging pediatric case scenarios in the quick diagnosis section.

The UTMJ serves as a forum for students to communicate research and clinical experiences. We encourage students to write articles in both basic and clinical sciences. As mentioned in issue one, the UTMJ will award several prizes to the articles published in this Volume. The winners of the awards will be announced in the next issue. We hope these will serve as a further incentive for students and members of the University of Toronto medical community to publish their work.

In order to improve the quality of the UTMJ we would appreciate feedback from our readers. Please send us your comments, submissions or concerns regarding the UTMJ and its contents.

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Beta-2 Blockers: Their Effects on Aqueous Production and Intraocular Pressure

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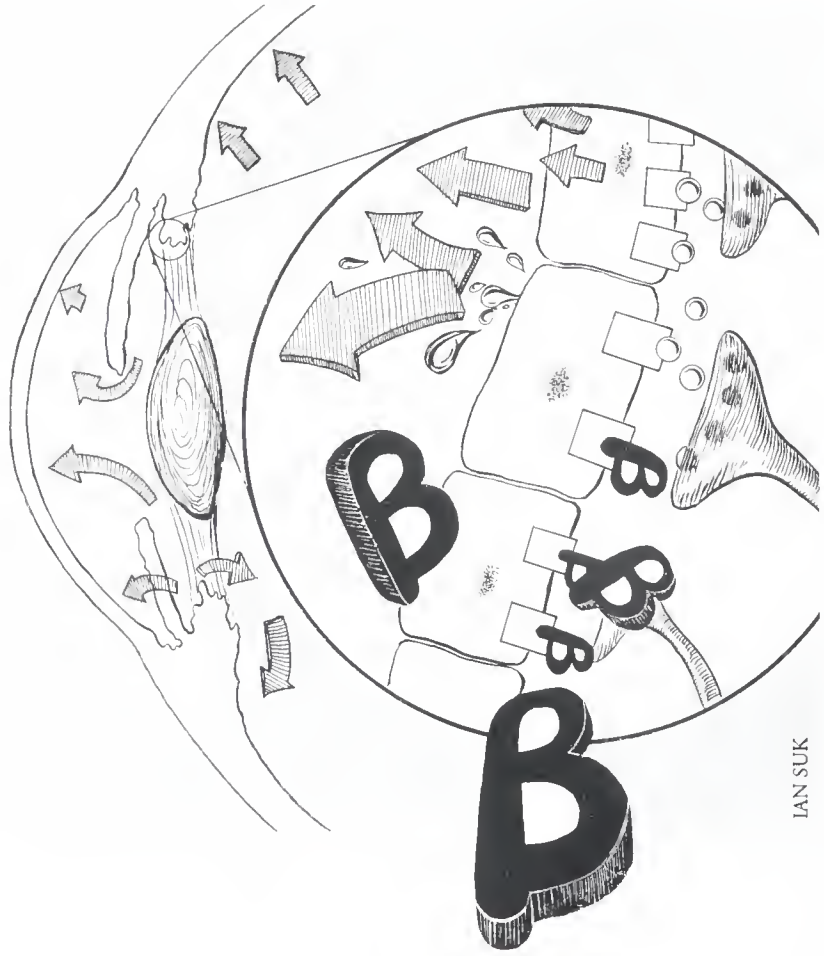
Abstract

Beta-2 adrenoceptors are known to exist in animal and human ciliary processes. The purpose of this study was to determine whether beta-2 blockers inhibit aqueous production and lower increased intraocular pressure (IOP). The results of the IOP recovery rate experiments (aqueous humor index) indicated that the beta-2 specific blockers IPS 339, LI 32-468 and ICI 118551 inhibited IOP recovery rate by 66%, 61% and 59% respectively. These beta-2 blockers also lowered IOP in rabbits with glaucoma. The results of this study indicate that beta-2 blockers may prove useful for patients with glaucoma.



Introduction

Aqueous humor is a clear, colourless fluid that is found in both the anterior and posterior chambers of the eye. The intraocular pressure (IOP) is maintained by balancing the rate of inflow of aqueous fluid with the rate of outflow of aqueous fluid. Aqueous humor is produced by the ciliary processes and secreted into the posterior chamber. It passes through the pupillary space to the anterior chamber where it is drained via the trabecular meshwork to the canal of Schlemm which then conducts it to the venous system.

Primary open-angle glaucoma is the most common form of glaucoma and is thought to be due to degenerative changes in the trabeculum, canal of Schlemm and adjacent channels which leads to an impedence to the outflow of aqueous fluid. Medical therapy is aimed at facilitating aqueous outflow through existing drainage channels and/or decreasing aqueous production by the ciliary processes.

Radioligand and other studies have confirmed the presence of beta-2 adrenoceptors in the ciliary processes of animals and man[1-3]. Furthermore, beta-2 antagonists bind to these receptor sites with high affinity[4].

The purpose of this study was to determine whether beta-2 blockers inhibit IOP recovery rate and lower IOP. Towards this end both normal and buphthalmic rabbits were used.

Methods and Materials

To determine the potential effects of beta-2 specific and other beta blockers on aqueous production, we used the IOP recovery technique (aqueous formation index) as described by Vareilles & Lotti(1987)[5]. Buphthalmic rabbits were used to determine the effects of beta-2 specific and other beta blockers on increased IOP[6].

1. Intraocular Pressure Recovery Method (aqueous formation index): Six pigmented rabbits were used to investigate each drug. A one-week washout period was used between experiments. All rabbits were accustomed to handling and to their restraint boxes in the laboratory environment for three days prior to the study.

IOP readings were obtained using a Digilab pneumatonometer which had been calibrated for rabbit eyes[7]. Pressure readings were taken three times and the mean used as a final IOP. One drop of topical anesthetic (proparacaine hydrochloride) was placed in the eye of each animal before IOP readings were measured.

Intraocular pressure was measured before installation of drug or buffer. Using a micropipette, 50 µL of drug was then instilled into each rabbit's lower conjunctival fornix. In the same manner, 50 µL of phosphate buffer was placed into the second eye of each animal. Drug and buffer administration were performed randomly in a double blind and masked fashion. IOP was remeasured 50 minutes later. A 23.4% solution of sodium chloride was then infused intravenously into each rabbit via a marginal ear vein at a rate of 1 mL/minute over a period of 10 minutes using a Sage pump. At the end of this infusion period intraocular pressures were measured at the following time intervals: 0, 5, 10, 20, 40, 60, 70, 80, 120, 130, and 140 minutes or until intraocular pressure recovered to pre-infusion values in one or both eyes.

A control experiment was initially performed as we anticipated a contralateral (consensual) response to the unilaterally applied drug. This control experiment was performed as described above, however buffer alone was placed in one eye. The same six rabbits were used throughout the study.

Compounds studied include three beta-2 specific blockers, namely IPS 339 (Dr. G. LeClerk, Strasbourg), LI 32-468 (Sandoz) and ICI 118551 (ICI-Pharmaceuticals, U.K.), a beta-1 specific blocker betaxolol hydrochloride (Betoptic, Alcon) and a non-specific beta blocker (-) timolol maleate (Timoptic, Merck Frosst). All compounds were either commercially prepared (Timoptic 0.5% and Betoptic 0.5%) or were freshly prepared as a 1% solution in phosphate buffer pH 7.4 (IPS 339, LI 32-468, ICI 118551).

2. Method to Determine the Effects of Beta Adrenergic Antagonists on Intraocular Pressure in Buphthalmic Rabbits: For this series of experiments five buphthalmic New Zealand albino rabbits were studied. All rabbits were allowed a minimum of three days to become accustomed to animal handling. Topical anesthesia was placed in the eye of each animal before intraocular pressure readings were measured.

Each rabbit was initially subjected to a diurnal pressure curve using a Digilab pneumatonometer over a 12-hour period from 7:00 a.m. to 7:00 p.m. These diurnal curves were used as the experimental control. A mean of three readings was taken to be the actual pressure. Control diurnal curves were performed within one week of each experiment and were repeated for each drug.

IOP was measured in both eyes of each animal 10 minutes before drug administration. At 7:00 a.m. (T = 0 minutes) 50 µL of drug or phosphate buffer was randomly administered in a masked fashion to one eye of each rabbit (the eye with the highest pressure). The second eye was not treated but its IOP was measured over the test period. IOP's were measured every 15 minutes for the first hour, every 30 minutes for the second hour and hourly for the duration of the experiment (12 hours). After the first hour of the experiment, the animals were returned to their cages. They were subsequently removed for each pressure check and then returned. The experiment was repeated a week later, alternating test drug and buffer.

A washout period of at least a week was allowed before each rabbit underwent further testing. Compounds studied in this section of the study included the beta-2 specific blockers IPS 339 (1%), ICI 118551 (1%) and LI 32-468 (1%). The non-specific beta blocker (-) timolol maleate (0.5%) and the beta-1 specific blocker betaxolol hydrochloride (0.5%) were also studied.

All animals were treated in accordance with the resolution of the Association for Research in Vision and Ophthalmology on the use of animals in research.

3. Analysis of Data: (A) The least squares method was used to determine intraocular pressure recovery rate (aqueous humor index over time for each rabbit). Analysis of variance of the change in IOP over time was performed. Comparisons were tested using the F test. (B) Analysis of variance was used to determine drug effects in buphthalmic rabbits.

The sources of variation considered were:

i) Variation among different rabbits

ii) Differences between the times of measurement

iii) Differences among the treated eye and opposite eye and the same control eyes

iv) Random variation

The test statistic used was the F statistic. The amount of random variation was used to estimate the standard deviation of the mean intraocular pressure for each time and treatment when required. A value of less than 0.05 was considered significant.

Three treatment effects were studied:

1. Differences among the three treatments, i.e., the treated eye and the corresponding control eye.

2. Changes occurring over time.

3. Interactions between treatment and time, i.e., was the difference (if any) between treatment the same at one hour after drug instillation as at two hours.

When examining short-term effects, the measurements at time 0 before any treatment was given, was used as a covariable thus controlling for the starting values of intraocular pressure in the analysis for all rabbit eyes. The

mean IOP readings at two hours were normalized as the mean result expressed as percentage of control.

Results

1. IOP Recovery Results (Aqueous Humor Index): Table 1 details the results (mean ± standard deviation) and statistical significance of the intraocular pressure recovery rate experiments (drug versus control). Of the five drugs tested, the beta-2 specific blockers IPS 339, LI 32-468 and ICI 118551 showed the greatest effect on IOP recovery rate. These three beta-2 blockers inhibited IOP recovery by 66%, 61% and 59% respectively. (-) Timolol maleate inhibited IOP recovery by 50% while the beta-1 blocker betaxolol hydrochloride inhibited IOP recovery by 42%. All of the above values were statistically significant.

Table 1: Results (mean ± standard deviation) of IOP recovery rate (aqueous humor index) of drug treated versus control group of rabbit eyes

Treatment	Slope of IOP recovery rate (mm Hg/min)	% Difference between drug vs control	P value
1) IPS 339	0.047 ± 0.003	-66.0	0.0001
Control	0.141 ± 0.007		
2) LI 32-468	0.055 ± 0.008	-61.0	0.0001
Control	0.141 ± 0.007		
3) ICI 118551	0.058 ± 0.004	-59.0	0.0001
Control	0.141 ± 0.007		
4) (-) Timolol Maleate	0.071 ± 0.007	-50.0	0.0001
Control	0.141 ± 0.007		
5) Betaxolol HCl	0.0827 ± 0.005	-42.0	0.0002
Control	0.141 ± 0.007		

$$\% \text{ difference} = \frac{(\text{slope of drug} - \text{slope of buffer or control}) \times 100}{\text{slope of buffer or control}}$$

Table 2 documents data derived from the buffer-treated second eyes versus drug treated eyes. IPS 339, LI 32-468 and ICI 118551 inhibited IOP recovery by 45%, 42% and 22% respectively. (-) Timolol maleate and betaxolol hydrochloride inhibited IOP recovery by 27% and 8% respectively. This data indicates that all 5 drugs produced consensual effects (see discussion).

Table 2: Results (mean ± standard deviation) of IOP recovery rate of drug treated versus buffer treated second eyes

Treatment	Slope of IOP recovery rate	% Difference between drug versus buffer	P value
1) IPS 339	0.047 ± 0.003	-45.0	0.004
Buffer	0.086 ± 0.005		
2) LI 32-468	0.055 ± 0.008	-42.0	0.004
Buffer	0.094 ± 0.008		
3) (-) Timolol Maleate	0.071 ± 0.007	-27.0	0.050
Buffer	0.097 ± 0.007		
4) ICI 118551	0.058 ± 0.004	-22.0	0.178
Buffer	0.074 ± 0.004		
5) Betaxolol HCl	0.0827 ± 0.005	-8.0	0.560
Buffer	0.089 ± 0.005		

2. Effect of Beta Blockers on Mean Intraocular Pressure in Buphthalmic Rabbits: Table 3 documents the effects of the five beta blockers on IOP. IPS 339 (1%) dropped IOP from 26 to 20 mm Hg (-6 mm Hg) (23%) within one hour of topical application. This drop in IOP was sustained over the 12 hour period of the study with a final IOP reading of 16.5 mm Hg. The contrast between the treated and diurnal control group of eyes was statistically significant over the 0-12 hour period.

LI 32-468 (1%) dropped mean IOP 21.8% in the glaucoma eyes from 31.6 mm Hg to 24.7 mm Hg (-6.9 mm Hg) within the first hour post treatment. This effect was sustained for 12 hours with a final IOP reading of 19.8 mm Hg. The contrast between the LI 32-468 treated and the diurnal control group of eyes was statistically significant over the 0-12 hour period of the study.

ICI 118551 (1%) dropped mean IOP 16.6% in the drug treated eyes from 24 mm Hg to 20 mm Hg (4 mm Hg) over the first hour of the study. This effect was sustained for 12 hours with a final IOP reading of 19.5 mm Hg. The contrast between the treated and diurnal control

group of eyes was statistically significant over the 0-12 hour period of the study.

(-) timolol maleate (0.5%) (Timoptic) dropped mean IOP 23.3% from 34.3 mm Hg to 25.7 mm Hg over the first hour of treatment (-8.6 mm Hg). This decrease in IOP was sustained over the 12 hour period of the study with a final IOP reading of 24.1 mm Hg. The contrast between the treated and control group of eyes was statistically significant over the 0-12 hour period.

This table also documents the effects of topical betaxolol hydrochloride (0.5%) (Betoptic) on buphthalmic rabbit IOP. As indicated, mean IOP dropped 23.3% from 31.7 mm Hg to 24.3 mm Hg after one hour (-7.4 mm Hg). This drop in IOP was sustained over the 12 hour period of the study with a final mean IOP reading of 21.6 mm Hg. The contrast between the treated and diurnal control group of eyes was statistically significant over this period of time.

Table 3: Effect of beta blockers on mean buphthalmic rabbit IOP

Drug	Initial Mean IOP	Mean IOP 1 Hour After Treatment	Final Mean IOP After Treatment
1) IPS 339	26.0 mmHg	20.0 mmHg	16.5 mmHg*
2) LI 32-468	31.6 mmHg	24.7 mmHg	19.8 mmHg*
3) ICI 118551	24.0 mmHg	20.0 mmHg	19.5 mmHg*
4) Timolol Maleate	34.3 mmHg	25.7 mmHg	24.1 mmHg*
5) Betaxolol	31.7 mmHg	24.3 mmHg	21.6 mmHg*

*($P < 0.05$) - Comparison between control vs treated group over 0-12 hours

Discussion

The purpose of this study was to determine whether beta-2 blockers inhibit aqueous production and lower increased IOP. Towards this end, two rabbit models were used. The IOP recovery technique described by Vareilles & Lotti (1987) is an indirect method of measuring aqueous production. It has previously been used to study the effects of various topical medications on aqueous production[8,9]. As indicated in Table 1, all of the beta blockers significantly inhibited IOP recovery with the beta-2 specific blockers showing the greatest effect. As indicated in Table 2, all of the beta blockers tested produced consensual effects on contralateral eyes. This effect was most marked with the beta-2 specific blocker ICI 118551, (-) timolol maleate (non-specific) and the beta-1 specific blocker betaxolol hydrochloride. Given that this consensual effect commonly occurs in animals and humans, a control experiment was used to obviate against this effect (Table 1). There are various theories as to why it occurs[10-13].

The results from the first part of this study suggest that all topical beta blockers inhibit rabbit aqueous humor production; with the beta-2 specific blockers showing the greatest effect. These results support the view that beta-2 adrenoceptors are involved in aqueous production[4].

The aim of the second part of the study was to determine whether beta-2 blockers lower intraocular pressure in rabbits with glaucoma. Buphthalmic rabbits respond to aqueous suppressant drugs in a similar manner to patients with primary open angle glaucoma[6]. The beta-2 specific blockers IPS 339, LI 32-468 and ICI 118551 all lowered buphthalmic rabbit IOP (Table 3). The mean one-hour drop in IOP was 23%, 22%, and 17% respectively. Furthermore, all three drugs lowered intraocular pressure for the duration of the study. Topical (-) timolol maleate (Timoptic) and betaxolol hydrochloride (Betoptic) are currently used to treat primary open angle glaucoma in both Europe and North America[13,14]. These results indicate that beta-2 specific blockers lower buphthalmic rabbit IOP in a similar fashion to drugs presently used to treat primary open angle glaucoma. Beta-2 blockers may therefore lower intraocular pressure in humans with primary open angle glaucoma.

There are a number of difficulties encountered when using buphthalmic rabbits to study drug effects on intraocular pressure. Firstly, IOP varies from day to day in buphthalmic rabbits. Secondly, buphthalmic rabbits often have asymmetrical pressures when the disease is bilateral. The consensual effect of a drug together with the asymmetry of pressures makes statistical comparison between the two eyes impossible. As a result, Vareilles et al (1980) in their drug studies on buphthalmic rabbits used initial IOP as the control level and IOP at various time intervals thereafter as the comparison levels. The problem with this method is that it presupposes that change in intraocular pressure is only due to drug effect, i.e., it neglects diurnal changes in intraocular pressure and is therefore potentially misleading. Even though diurnal curves varied in our study, we used diurnal curve controls rather than initial IOP's or second eyes for reasons

described above. Further tonometric studies are in progress to determine whether acute drug effects can be accurately evaluated using early morning pressures as baseline rather than diurnal curves. Other problems reported and experienced using the buphthalmic rabbit model are:

1. Buphthalmic rabbits are not readily available and have to be specially bred.

2. The gene for buphthalmos is semilethal and therefore the rabbits do not survive well[15].

3. Examination of the fundi of these animals is not possible due to the cloudy cornea; therefore, it is not possible to conduct long-term ophthalmoscopic studies to determine whether a drug under investigation prevents optic nerve damage.

Despite these problems the buphthalmic rabbit model remains a useful model of ocular hypertension. Further work is required to determine diurnal variation and seasonal variation on diurnal curves in buphthalmic rabbit eyes.

In conclusion, our results are consistent with the view that beta-2 receptors are directly or indirectly involved in aqueous production. Beta-2 blockers both inhibit rabbit aqueous production and lower IOP. Beta-2 blockers may prove useful for treatment of human glaucoma, particularly in patients with cardiac disease.

Acknowledgements

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References

1. Nathanson JA. Adrenergic regulation of IOP: Identification of beta-2 adrenergic stimulated adenylate cyclase in ciliary process epithelium. Proc Natl Acad Sci USA 77,12:7420-7424, 1980.

2. Trope GE, Clark B. Beta adrenergic receptors in pigmented ciliary processes. Brit J Ophthalmol 67:557-558, 1982.

3. Wax MB, Molinoff P. Distribution and properties of B-adrenergic receptors in human iris, ciliary body. Invest Ophthalmol Vis Sci 83:420-429, 1987.

4. Trope GE, Clark B. Binding Potencies of 3 new beta blockers to the ciliary processes and the possible relevance of these drugs to intraocular pressure. Brit J Ophthalmol 68:245-247, 1984.

5. Vareilles P, Lotti VJ. Effect of Timolol on aqueous humor dynamics in the rabbit. Ophthalmic Res 13:72-79, 1987.

6. Vareilles P, Conquet P, Lotti VJ. Intraocular pressure response to antiglaucoma agents in spontaneous buphthalmic rabbits. Ophthalmic Res 12:296-302, 1980.

7. Goldberg M. Dopaminergic effects on intraocular pressure and binding in ciliary processes. MSc Thesis U of T p.63E, 1987.

8. Chiou GCY. Ocular hypotensive effect of Haloperidol a dopaminergic antagonist. Arch Ophthalmol 102:143-145, 1982.

9. Chang FW, Burke JA, Potter DE. Mechanism of ocular hypotensive action of ketanserin. J Ocular Pharm 1(2):137-147, 1985.

10. Shin DH. Bilateral effects of monocular Timolol treatment. Am J Ophthalmol 102:275-276, 1986.

11. Liu JH, Neufeld AH. Study of central regulation of intraocular pressure using ventricular perfusion. Invest Ophthalmol Vis Sci 26:136-143, 1986.

12. Woodward DF, Dowling ML, Feldman BJ, Chen J. Topical Timolol at conventional unilateral doses causes bilateral ocular beta blockade in rabbits. Exp Eye Res 44:319-329, 1987.

13. Novack GD. Ophthalmic beta blockers since Timolol. Surv Ophthalmol 31, 5:307-329, 1987.

14. Leopold I, Duzman E. Observations on the pharmacology of glaucoma. Am Rev Pharm Tox 26:401-428, 1986.

15. Hanna BL, Sawin PB, Sheppard J. Recessive buphthalmos in the rabbit. Genetics 47:519-529, 1962.

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Mitral Valve Replacement: The Search for the Ideal Prosthesis

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Abstract

Since artificial heart valves were first implanted in humans during the late 1950's and early 1960's, many design and structural modifications have been made. Prosthetic valves are broadly classified into two groups: tissue valves, either porcine or bovine and mechanical valves. The use of these valves varies considerably between different centers which serves to emphasize that the perfect heart valve substitute has yet to be found. This paper presents an historical perspective of the use of prosthetic valves in mitral valve replacement (MVR) with reference to the University of Toronto experience with MVR.

ELIZABETH ROWAN

Introduction

The surgical treatment of mitral valve disease has progressed significantly over the past forty years and has paralleled the remarkable advances in cardiovascular surgery. Emerging from the seemingly crude, but effective, closed mitral valve commissurotomies, a wide variety of open heart procedures now exist. This includes the repair of diseased valves as well as valve replacement with insertion of prosthetic devices.

The first attempts at artificial mitral valve replacement in humans took place in the late 1950's[1]. The valves consisted of Teflon fabric leaflets with a film of polyurethane and artificial chordae tendinae. These valves were an attempt to maintain the anatomic configuration of the natural valve. Major problems centered around inadequate coaptation of the valve leaflets with regurgitation as well as severe thromboembolic sequelae.

During the 1960s, several characteristics were delineated which served to define the ideal prosthetic valve (Table 1). Although many design modifications have taken place, these basic criteria have still not been completely met[2]. There exists today, as in the 1960s, two broad categories of artificial heart valves - namely mechanical and tissue, with each having their own specific advantages and disadvantages.

Table 1: Characteristics of an ideal prosthetic valve

1. It must not form a thrombus and thus propagate emboli.
2. It must be chemically inert and not damage blood elements.
3. It must offer no resistance to physiological flows.
4. It must close promptly and remain closed during the appropriate phase of the cardiac cycle.
5. It must open promptly and remain open during the appropriate phase of the cardiac cycle.
6. It must remain durable.
7. It must be technically easy to insert and be capable of permanent fixation.

As improvements occurred in the design of these valves, surgical preference oscillated between the tissue valves and the mechanical prostheses. Even today, there exists no clinical justification for the exclusive use of either type of valve.

The Starr-Edwards Valve

The first mechanical prosthesis implanted at the University of Toronto was the Starr-Edwards ball and cage valve. This valve consisted of a metal cage and a silastic ball which acted as the occluder (Fig. 1). The high thromboembolic consequences of such a device led to the introduction of a cloth covering on all exposed metal parts, but even this modification failed to adequately prevent thromboemboli and thus patients were required to maintain lifelong anticoagulation with all of the associated risks. In addition to emboli, the interface between the cloth and native tissue provided a remarkable substrate for thrombus propagation and case reports of ball obstruction with functional stenosis or regurgitation began to appear in the literature[3]. The cloth covering was also associated with hemolysis. An uncommon complication of the Starr-Edwards valve was erosion into the left ventricular wall with endocardial fibrosis, scarring and sometimes aneurysmal formation[3].

Figure 1: The Starr-Edwards "model 6120" ball and cage valve

Other major disadvantages of this valve design included its bulky, high profile with resulting left ventricular outflow obstruction, relatively large flow gradient across the valve, hemolysis due to turbulence around the ball and non-physiological flows[1]. This latter problem was detected when it was found that the circumferential flow around the ball was the primary factor in turbulent hemolysis and the gradient across the valve2.

Despite these flaws, the Starr-Edwards valve has proven to be a prototype in terms of valve durability and it is not unusual to see patients alive and well as many as 20 years after their initial mitral valve replacement.

Autogenous Fascia Lata Valves

Given the complications associated with the Starr-Edwards valve, it was not surprising that the introduction of tissue valves created much excitement among surgeons. Tissue valves offered distinct advantages over mechanical valves. In particular, they had physiological central flow orifices, they were non-obstructive, they caused little hemolysis and they had low thrombogenicity which allowed patients to discontinue anticoagulation. The first bioprosthetic valve replacement using a tissue valve employed autogenous fascia lata. Senning's original technique of valve preparation could only be utilized in the aortic position, but in 1969 a method of fixation of the fascia lata valve to a rigid frame was described[4] so that it became possible to replace any cardiac valve with a fascial valve.

Short-term results were optimistic in both the aortic and mitral positions, but by 1971 the durability of these valves came into question, especially when used in the mitral position. Subsequent studies confirmed this finding and the three year failure rate of fascial mitral valves were reported to be 90-95%[4]. In addition, regurgitant flow was seen as early as 2 months post-operatively. Pathologic findings included bacterial endocarditis, fibrosis, calcification, commissural fusion and cartilaginous formation in the fascia lata valves[3].

In 1970, an international roundtable on fascia lata valves was held in Toronto under the aeges of Drs. Trimble, Bigelow and Silver[5]. This produced a co-operative international study and a central registry to provide a long-term follow up of the use of these valves. Even at this time it was recognized that the use of fascia lata valves for mitral valve replacement was controversial.

Disc Valves

As the optimism surrounding fascia lata valves began to fade, interest once again shifted towards mechanical valves. The problems of circumferential flow, high profile, transvalvular gradients, hemolysis and thromboembolism of ball valves were partially offset by the introduction of disc valves[1]. Prostheses implanted at the University of Toronto included the Beall and the Bjork-Shiley tilting disc valves. These valves consisted of a flat or spherical disc occluder mounted on metal struts or hinges which tilted open and closed during the appropriate phase of the cardiac cycle. This design created semi-central flow and thereby greatly reduced hemolysis as well as the transpros-

Figure 2: The Bjork-Shiley spherical disc valve

thetic pressure gradient. In addition, the struts of these valves were much smaller than those of the ball and cage type and therefore gave these valves a much lower profile once inserted (Fig. 2). This property was immensely important in patients with hypertrophic left ventricles and/or small left ventricular cavities, as in mitral stenosis. This design also allowed the surgeon to implant a prosthesis with a much greater orifice area than was previously permitted with the high profile valves.

Unfortunately, the problems of thrombogenicity were still not adequately controlled and patients still had to receive lifelong anticoagulation. The advent of pyrolytic carbon coating was a significant improvement, but still demanded anticoagulants. A particular problem of the tilting disc valves was that there remained areas of blood flow stasis on the valve - even during valve motion - and these areas promoted thrombus formation which led to disc occlusion and sometimes to sudden and severe consequences[1].

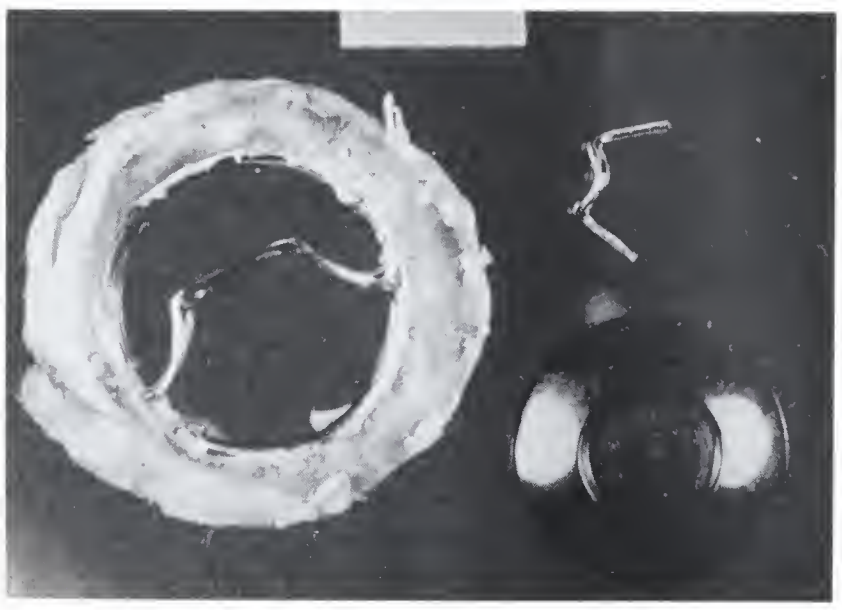

Figure 3: Strut fracture in the Bjork-Shiley disc valve

There were also case reports of strut fracture and disc embolisation resulting in sudden death. These were due to metal fatigue and newer designs strived to reduce the stresses on the struts and hinges of these valves (Fig. 3). Although the fracture rates were in the order of 7 in 10,000, the often catastrophic consequences attracted much media publicity and surgeons became reluctant to use these valves.

Another uncommon complication of tilting disc valves is disc entrapment on remnant valvular structures (e.g.-chordae). This necessitated the complete removal of all native structures prior to insertion of the valve. Later studies by David and coworkers[6,7] have proven the importance of the chordae tendinae and papillary muscles in the preservation of left ventricular function. This finding precluded surgeons from implanting mechanical valves in patients with poor pre-operative left ventricular function.

Porcine Valves

The introduction of formaldehyde and then gluteraldehyde preserved porcine valves once again piqued interest in the use of tissue valves. Two models - the Carpentier-Edwards and the Hancock - of xenograft valves were successfully implanted at the University of Toronto. The new techniques of valve preservation did manage to improve the durability of tissue valves but they were still far from ideal.

With time the collagen fibres in the transplanted tissue degenerate and loosen, making cusps prone to rupture or incompetence[3]. In addition, the degenerated collagen in tissue valves can become calcified, thereby thickening and stiffening the cusps and rendering the valve stenotic[3].

This process of calcification has proven to be accelerated in children and young patients (those less than 35 years of age) - due presumably to the enhanced calcium metabolism in these patients. Nevertheless, the average longevity of these valves in the mitral position was 8-10 years and these valves proved to be a significant improvement in design and the avoidance of anti-coagulation made them popular substitutes for several years. Figure 4 shows the Carpentier-Edwards valve prior to implantation and figure 5 is an example of the same valve suffering from degeneration.

Ionescu-Shiley Pericardial Valve

The Ionescu-Shiley pericardial valve was designed to alleviate some of the problems surrounding other tissue valves during the late 1970's. The design of the valve

Figure 4: The Carpentier-Edwards xenograft valve

allowed simultaneous opening of the leaflets and hence a smooth non-turbulent flow. This feature also resulted in lower residual transvalvular gradients and a lower profile than porcine valves[8]. Unfortunately, this valve was prone to a peculiar degenerative change and widespread reports of valve failure began to occur. The specific pathology involved a cuspal tear at the base of the stent and despite the belief that tissue valves degenerate gradually, patients began presenting in acute mitral insufficiency secondary to valve failure approximately four to seven years post-operatively.

Bjork-Shiley Tilting Disc Valve

Since the introduction of the Bjork-Shiley tilting disc valve in 1969, the prosthesis has undergone several successive modifications to improve its hemodynamic performance and diminish thromboembolic complications[9]. The design of a valve with a convexoconcave disc reduced stasis of blood on the disc and thus lowered the thrombogenicity of the device. Progressive changes in the opening angle led to the 60 degree and then the 70 degree convexoconcave valve. However, the strut fractures reported with the original tilting disc valve began to appear with alarming frequency in the 70 degree model and it was subsequently removed from the market. However, the hemodynamic advantages of the 60 degree convexoconcave model were preserved.

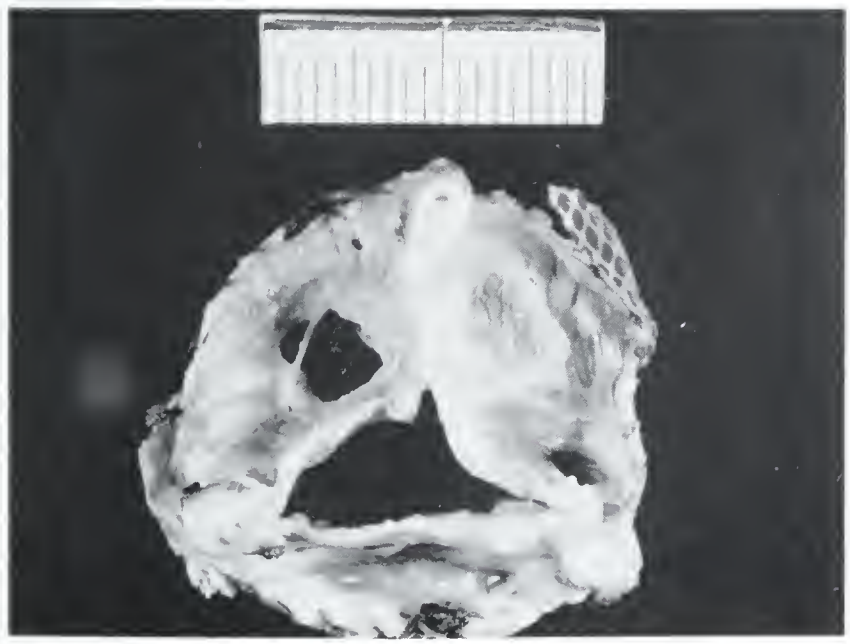

Figure 5: Leaflet tear in the Carpentier-Edwards xenograft valve

The problems of metal fatigue and strut fracture were largely offset by the design of the monostrut valve. This prosthesis, introduced in 1982, incorporated a single metal strut which was made an integral part of the cage. The disc remained convexoconcave and opened to 70 degrees. This valve has proven to be effective and is still widely used today.

Modern Tissue Valves

Tissue valves in use today include the Hancock II, Carpentier-Edwards and Intac porcine valves along with the Carpentier-Edwards bovine pericardial valve. All of these valves have attempted to improve upon the durability of bioprostheses. Reports from the current literature quote a ten year freedom from failure of approximately 60%[10].

The technological improvements in the manufacturing of these valves have focused on improved preservation techniques. Low-pressure fixation has shown to be less harmful to the collagen meshwork of the valve leaflets and hence reduces the degenerative changes. Methods of rendering these valves calcium free by impregnation with a calcium retardant have also been developed in the hope of using bioprosthetics in younger age groups.

In addition, design modifications have lowered the profile of these valves and thereby reduced the transvalvular flow gradients. These valves are more popular when used in the aortic position due to their better durability, but are still highly effective and widely used in mitral valve replacement.

St. Jude Medical Bileaflet Valve

Introduced in 1977, the St. Jude bileaflet valve is a significant design modification from other existing mechanical valves (Fig. 6). Fully coated in pyrolytic carbon, this valve had no obvious struts and consisted of two 'D'-shaped discs which closed to occlude the orifice[3]. The major advantages of this design are its very low profile, low thrombogenic rate (although it still requires anticoagulation) and excellent hemodynamic profile. One feature that distinguishes this device from other

mechanical valves is its ability to be implanted in the presence of a preserved native mitral valve. This has obvious implications regarding its use in patients with poor pre-operative left ventricular function.

One disadvantage of this valve involves its implantation. Current reports indicate the valve commissure should be implanted perpendicular to the ventricular septum, but that the leaflets should be probed after insertion to insure mobility. Unfortunately, in the event the discs are

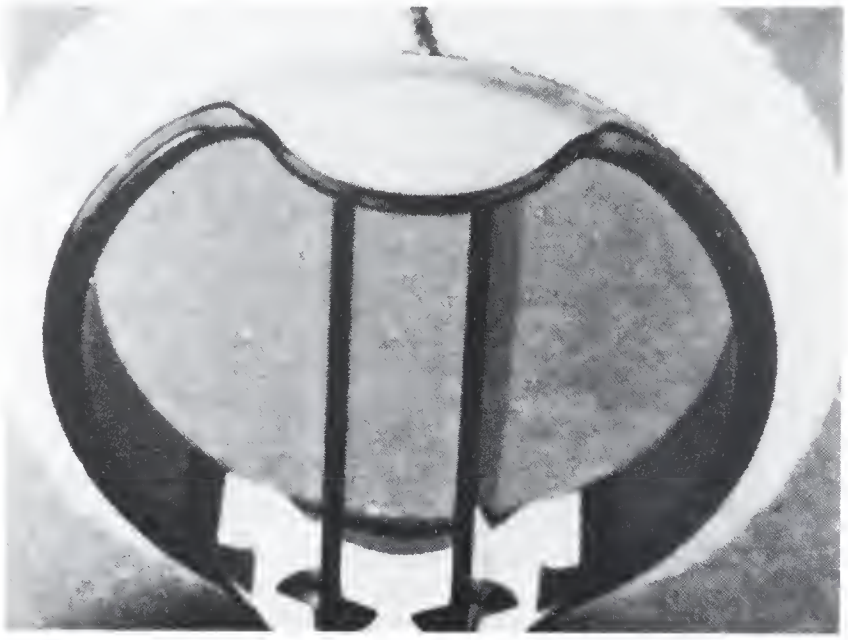

Figure 6: The St. Jude medical bileaflet valve

obstructed, the valve cannot be rotated in its sewing ring, necessitating complete removal of all sutures in order to re-implant the valve. The resultant increase in bypass time and aortic cross clamp time (the period in which the ascending aorta is clamped) significantly increases the patient's risk of peri-operative injury.

A newer valve design - the Carbomedics bileaflet valve - attempts to correct this problem by allowing full rotation of the valve within its sewing ring, but this feature has impinged upon the valve's orifice area and has increased the peak diastolic flow gradients.

Conclusion

Since the advent of artificial mitral valve replacement in the 1950's, there have been several significant discoveries in the search for the ideal prosthetic substitute. Major advances in surgical technique and in prosthetic design have taken place at the University of Toronto and around the world. There still exists two categories of prostheses, namely mechanical and tissue and both have their specific advantages and disadvantages. The major problem with mechanical valves continues to be the rate of thromboembolism and the need for anticoagulation with

Table 2: Comparison of prosthetic mitral valves

	Thrombogenicity	Structural Valve Failure	Transvalvular Flow Gradient
Starr-Edwards	++++	+	+++
Fascia Lata	+	++++	++
Early Disc Valves	+++	++	++
Hancock I Porcine	+	+++	++
Ionescu-Shiley Pericardial	+	++++	++
Bjork-Shiley Monostrut	++	+	++
Hancock II Porcine	+	++	++
St. Jude Bileaflet	++	+	+

all of its inherent risks. Tissue valves - whether porcine or bovine - still have questionable longterm durability. Table 2 is a comparison summary illustrating the various strengths and weaknesses of the valves implanted at the University of Toronto.

There exists several relative indications for the use of one valve type over another in certain clinical situations, but to date there has not been justification for the exclusive use of either mechanical or tissue valves on the basis of patient mortality or morbidity.

Figure 7 illustrates the proportion of valvular surgery at Sunnybrook Health Science Centre, a major Toronto teaching hospital. Approximately twenty percent of all open heart procedures (pumps) involve valve

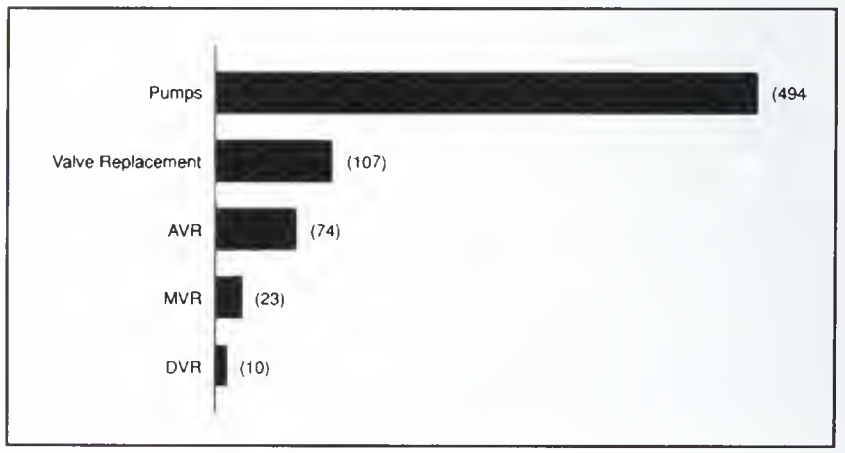

Figure 7: Mitral valve replacement at Sunnybrook Health Science Center (1990)

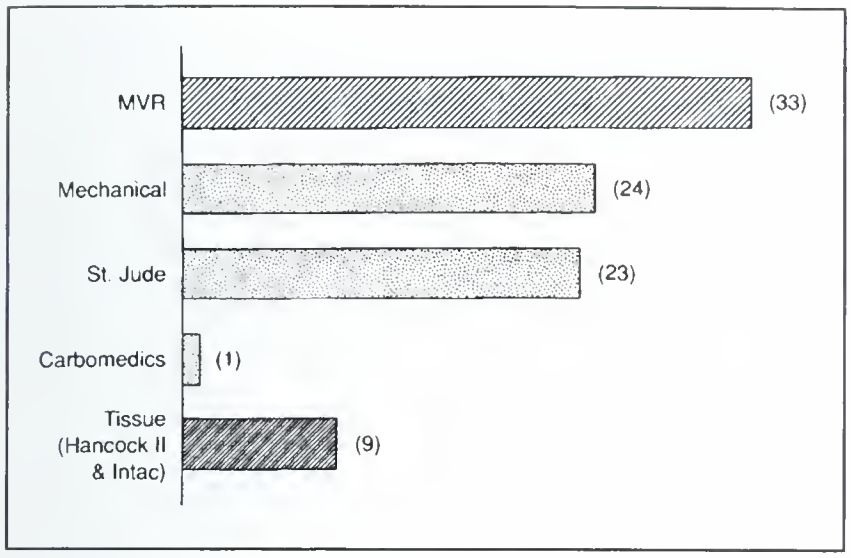

Figure 8: Prostheses used during mitral valve replacement at Sunnybrook Health Science Center (1990)

replacement. Figure 8 reveals the type of prosthesis implanted in the mitral position. Mechanical valves were implanted in 24 of 33 patients undergoing mitral valve replacement, while tissue valves were used in the remaining 9 patients. At present the St. Jude bileaflet valve seems to be the most popular mechanical valve and as such is being implanted with increasing frequency in more centers around the world. Current research is aiming towards the creation of a non-thrombogenic mechanical valve, one which will hopefully alleviate the need for anticoagulation[16]. In the meantime, clinical trials are underway to determine if low dose coumadin therapy can maintain adequate anticoagulation[17]. As figure 8 indicates the current trend is to use mechanical valves for prosthetic replacement of the mitral valve. This trend will continue until the introduction of tissue valves with significant improvements in durability. Until then, the search continues for the ideal prosthetic valve.

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References

1. Smeloff EA. Comparative study of heart valve design in the 1960's. Ann. Thorac. Surg. 1989; 48: S31-2

2. Harken DE. Heart valves: Ten commandments and still counting. Ann. Thorac. Surg. 1989; 48: S18-19

3. Silver MD, Wilson GJ. Pathology of cardiovascular prostheses including coronary artery bypass and other vascular grafts. Cardiovascular Pathology. New York: Churchill Livingstone, 1983

4. Editorial. Obituary for fascia lata heart valves. British Medical Journal 1976; 1: 115-116

5. Trimble AS. First international roundtable on fascia lata heart valves. Surgery 1972; 71: 10-14

6. David TE, Uden DE, Strauss HD. The importance of the mitral apparatus in left ventricular function after correction of mitral regurgitation. Circulation 1983; 68(suppl II): II-76

7. Miki S, Kusuhara K et al. Mitral valve replacement with preservation of chordae tendinae and papillary muscles. Ann Thorac Surg 1988; 45: 28-34

8. Gonzalez-Lavin L, Tandon AP et al. The risk of thromboembolism and hemorrhage following mitral valve replacement. Journ Thorac Cardiovasc Surg 1984; 87: 340-51

9. Thulin LI, Bain WH et al. Heart valve replacement with the Bjork-Shiley Monostrut Valve: Early results of a multicenter clinical investigation. Ann Thorac Surg 1988; 45: 164-70

10. Hammermeister KE, Henderson WG et al. Comparison of outcome after valve replacement with a bioprosthesis versus a mechanical prosthesis. Initial 5 year results of a randomized trial. Journ Amer Coll Card 1987; 10(4): 719-32

11. Braunwald NS. It will work; The first successful mitral valve replacement. Ann Thorac Surg 1989; 48: S1-3

12. Kay EB. Early years in artificial valve development. Ann Thorac Surg 1989; 48: S24-5

13. Geha AS. Long-term outcome of cardiac valve substitutes. Ann Thorac Surg 1987; 44: 566-67

14. Carpentier A. From valvular xenograft to valvular bioprosthesis: 1965-70. Ann Thorac Surg 1989; 48: S73-4

15. Davila JC. Where is the ideal heart valve substitute? What has frustrated its realization?. Ann Thorac Surg 1989; 48: S20-3

16. Rao V, Tong CP et al. Mitral valve replacement: Mechanical versus bioprosthetic valves - A clinical review. Can. Journ. Card. 1991; 7(6): 259-64

17. Thulin LI. Quality of life in patients with mechanical heart valve prostheses. Doctoral Dissertation, Lund University, Sweden, 1988.

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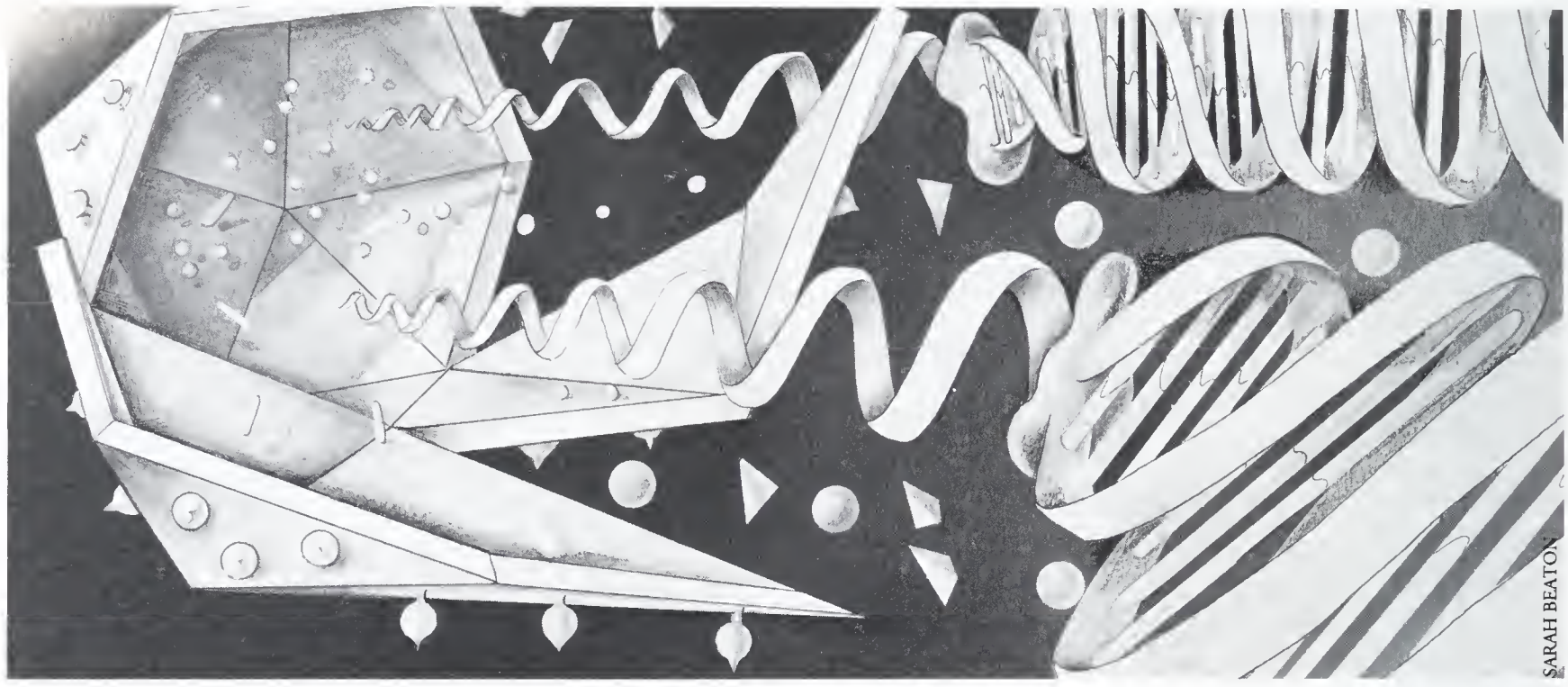

The Development of A Vaccine for the Prevention of Acquired Immunodeficiency Syndrome: Prospects and Pitfalls

Scott Young, Ph.D., 9T3 and Edward Y.W. Yu, B.Sc., 9T3

Abstract

Addressing the threat to human health posed by the human immunodeficiency virus (HIV) is one of the greatest challenges to modern medicine. This infectious agent is responsible for the acquired immunodeficiency syndrome (AIDS), a disease associated with striking morbidity and mortality. Progress has been made in the development of anti-HIV therapeutics, however, an important objective of medicine remains the prevention of disease. This report examines the strategies which are being used to develop a HIV vaccine and considers some of the technical, biological and ethical problems encountered to date.

Introduction

Acquired immunodeficiency syndrome (AIDS) was first recognized in 1981[1] as a new disease characterized by immunosuppression. The etiologic agent was subsequently isolated and identified as a virus now referred to as human immunodeficiency virus (HIV)[2,3]. During the early onset of the epidemic in North America, AIDS was associated with the male homosexual population. Other groups, including intravenous drug addicts, hemophiliacs, blood transfusion recipients prior to 1985, Haitian-Americans and sexual partners of the above, have since been identified to be at increased risk for this disease as well. Figures compiled in 1990 by the World Health Organization estimate that between 6-8 millions people world -wide are HIV-infected, which represents about 1 in every 400 adults alive[4]. It is estimated that there are at present 1.5 million people infected with HIV in the U.S. alone[5]. Since an effective cure for the disease is not yet available, there is a pressing need to develop a vaccine against HIV infection.

The HIV Virion and its Pathogenesis

The human immunodeficiency virus belongs to a large family of viruses known as the retroviridae. The life cycle and molecular biology of HIV-1 is now fairly well understood and details of these processes have been described in a recent review[5]. This family of viruses is characterized by having a diploid RNA genome and possession of the polymerase enzyme, reverse transcriptase. These viruses have the unique capability of using the reverse transcriptase to synthesize DNA

transcripts from their RNA template and to integrate this transcript into the genome of the infected host cell. Morphologically the HIV virion is roughly spherical and has an envelope made of lipid membrane with spike-like surface glycoprotein molecules (env) inserted in it (Fig. 1)[6,7]. The core consists of several proteins and a capsid containing the diploid RNA and the polymerase reverse transcriptase.

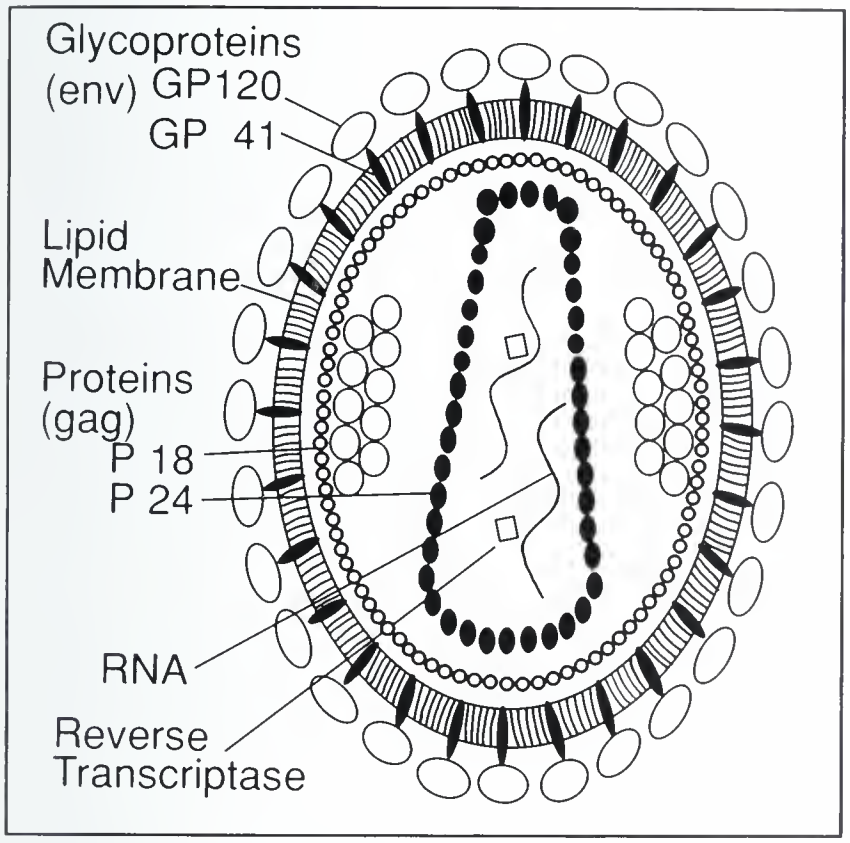

Figure 1: Morphology of HIV-1 and diagram of the structural relation of major viral proteins.

HIV infection occurs by direct inoculation of infected body fluid or cells. The four major routes for transmission are: i) sexual, ii) use of contaminated needles, iii) transfusion of infected blood or blood products, and iv) from an infected mother to her infant in utero or through breast milk. After initial exposure to HIV, 20 - 50% of individuals who eventually seroconvert develop symptoms of an acute illness within a few weeks characterized by fever and lymphadenopathy which is self-limiting. This phase is then followed by a latent period ranging from 9 months to 7 years during which the patient is symptom free. Onset of AIDS is marked by manifestations of immune deficiency, with the patient beginning to suffer from opportunistic infections and, in many cases, developing an otherwise rare form of sarcoma (Kaposi's). At the present time, 90% of AIDS patients in North American die two years after onset of the disease[8].

The pathogenesis of HIV is believed to be largely produced through cytotoxic mechanisms affecting specific subpopulations of cells. The most prominent feature of the disease, immunosuppression, results from infection of T helper cells and antigen-presenting cells which bear the CD4 surface antigen. This has been attributed to the binding of the HIV envelope protein gp120 to CD4 antigens on host cells followed by fusion and endocytosis of the virus[9]. However, other symptoms are produced after infection of non-CD4 cells, such as chromaffin cells of the GI tract and glial cells of the brain. Cell death appears to result from a number of processes, which include: i) disruption of cell membranes during the 'budding' phase of viral replication, ii) gp120-mediated fusion of T helper cells leading to the eventual formation of a moribund syncytium, iii) lysis of infected host cells by either NK or cytotoxic $CD8^+$ T lymphocytes, and iv) antibody-dependent cell mediated cytotoxic lysis of uninfected T helper cells which bind free gp120[10].

Principles of Vaccination

Vaccination is the process whereby an individual is inoculated with an antigenic preparation (vaccine) to stimulate the immune system so that on a subsequent encounter with a specific infective organism, a stronger, faster and more protective immune response can be elicited.

The principle of vaccination is based on the ability of the body's immune system to 'remember' prior exposure to a foreign antigen. This is due to clonal expansion of populations of antigen-specific B and T lymphocytes and the formation of memory cells which are capable of responding to that antigen in the future. The objective in the development of a vaccine is to produce an agent which mimics the antigenicity of the pathogen but which does not produce the disease state or have any other toxic side effects. The critical determinant of the efficacy of any vaccine is its ability to generate appropriate memory cells, so that the response upon challenge with the pathogen is rapid and effective.

A good vaccine should produce strong humoral as well as cellular responses from the immune system. This is especially true in the development of an HIV vaccine because the virus can be introduced via several different routes. Transmission by needle-stick or blood transfusion is usually due to contamination with HIV-infected cells, while transmission after sexual contact and transplacental infection most often involves exchange of free virus particles. Spread of the infection within the host may result from release of free virus from cells, but may also proceed by fusion of an infected cell with an uninfected one. The immune system must be able to clear the body

both free virus (through antibody binding and opsonization) and infected cells (destroyed by cytotoxic T lymphocytes or antibody-dependent cell-mediated cytotoxicity).

Specific Approaches to the Development of an AIDS Vaccine

HIV Genomic Products as Immunogens and Methods of Presentation: HIV particles and host cells infected with HIV express an antigen on their surfaces which is the viral env protein or gp160 (a CD4 molecule receptor; see Fig.1). This protein is encoded by the HIV genome and should be recognized by the immune system as being 'non-self'. This exposed antigen represents an ideal molecule which might serve as the basis for immunization. Indeed, cytotoxic T cells directed against this antigen have been detected in seropositive individuals[11]. The HIV virion is also composed of a number of other 'non-self' proteins which perform either structural or enzymatic functions. These products might also be used for vaccination since fragments of these antigens can make their way to the surface of infected cells.

Several approaches to presenting viral antigens for the purpose of immunization have been devised[12], and the proposed vaccines can be classified according to the nature of the immunogen: 1) live virus (either attenuated or recombinant), 2) inactivated virus, 3) recombinant DNA products, 4) natural subunit products, 5) synthetic peptides, and 6) anti-idiotypic antibodies. The strengths and weaknesses of these different strategies will be briefly reviewed.

1. Live Viruses: This approach uses non-pathogenic, yet replication-competent, viruses to sensitize the host to HIV antigens. This might be attempted using an attenuated (non-pathogenic) strain of the HIV, which might be isolated after selection or modification. A vaccine based on this method should be highly immunogenic, since it would present both T cell and B cell epitopes. This represents a potentially hazardous approach for two reasons: i) genetic instability may lead to the generation of a virulent (pathogenic) strain of immunizing virus, and ii) retroviral insertion into the host's genome may produce activation of cellular oncogenes and subsequent malignant transformation.

A second approach which makes use of live viruses is immunization with recombinant viruses. This involves infection of the subject with a non-pathogenic virus carrying an inserted HIV sequence, which acts as the immunogen. Under these conditions, there is no chance of HIV infection since only a small portion of the HIV genome is present. Nonetheless, the vector virus might produce complications, especially in immunocompromised subjects. It is also possible that the vaccine would be ineffective in subjects who had immunity to the carrier virus.

The most suitable candidate for incorporation into the vector would be the env gene because it expressed on the external surfaces of virus particles and infected cells. However, there is a serious problem with using this molecule as the immunogen, and this applies to all other approaches which intend to use this molecule as a target. The gp120 portion of the env protein is encoded by a sequence which is hypermutable, and with each round of replication there is a high probability that the env protein will change and hence evade any mounted immune response. It is therefore virtually impossible to produce vaccines based on the env protein which account for this polymorphism, unless a highly conserved region of the gp120 can be found. Recent studies have found that the vaccinia virus recombined with either the pol (reverse transcriptase) gene[13] or the gag (nucleocapsid) gene[14] can produce immune responses in experimental systems. These results are encouraging because the pol and gag sequences are more highly conserved.

2. Inactivated Virus: Immunization can be achieved after inoculation with virus killed by exposure to radiation or chemicals. This approach has been successful with diseases such as polio and influenza. The preparations are easy to produce and have the potential for high immunogenicity. The inactivation procedure must be 100% effective or residual RNA activity could lead to HIV infection. However, under these stringent conditions of inactivation, the viral antigens may become denatured and hence not induce an appropriate immune response.

3. Recombinant Subunit Vaccines: The entire genome of the HIV has been cloned and sequenced[5], and hence specific genes can be used to produce large amounts of viral proteins which may serve as vaccine. Bacteria transfected with a single gene is most often used to produce genetically-engineered protein, however better post-translational modifications of HIV proteins are obtained when the genes are expressed in eukaryotic cells (e.g. yeast or mammalian). This approach has been used for immunization against the hepatitis B virus, where the HBsAg is synthesized by recombinant DNA technology. While there is no chance of HIV infection with this method, env polymorphism complicates the use of recombinant gp120 as the immunogen.

The results of a Phase I clinical trial which evaluated the safety and immunogenicity of a recombinant gp 160

(transmembrane protein consisting of 120 and 41 subunits) vaccine in subjects who were already seropositive for HIV have been recently reported[15]. This study found that repeated inoculations with gp 160 was not associated with any significant systemic toxicity, although some minor local reactions to injection were noted. Augmentation of gp 160 specific humoral and cellular immune responses were observed in over half (63%) of the subjects. These results are promising and demonstrate the potential value of this approach in inducing protective immunity.

4. Natural Subunit Products: Proteins extracted from virus preparations represent yet another potential source of vaccine. Specific subunits of proteins (e.g. gp120), produced by enzymatic treatment, should be highly immunogenic since they represent native antigens. There would be no chance of HIV infection with these extracts. However, the purification procedures would make this class of vaccine expensive, which is a major disadvantage for distribution to developing countries.

5. Synthetic Polypeptides: Oligopeptides, synthesized from amino acid precursors, which represent sequences of HIV protein may prove to be particularly useful for immunization. These reagents are being developed in an effort to determine the most immunogenic, yet conserved, regions of the env protein[16]. There is no chance of HIV infection with this approach, however the small size of the polypeptides makes them poorly immunogenic, and vaccines of this nature will require the use of adjuvants or carrier proteins.

6. Anti-idiotype Antibodies: This novel approach involves inoculation with antibodies targeted to the variable regions of antibodies directed against viral antigens. These reagents act as an 'internal image' of the antibody binding site, and hence mimic the antigen. An example of this would be immunization with anti-CD4 which should theoretically result in an immune response against gp120. There is no chance of HIV infection since the immunogen is an antibody, however use of anti-CD4 would again be complicated by env polymorphism.

Additional Difficulties in Developing an HIV Immunization Protocol

It is not clear which of the above approaches (if any) will lead to a successful HIV vaccine. Those without risk of iatrogenic HIV infection are obviously the most desirable, but often these reagents are poorly immunogenic or cannot compensate for viral protein polymorphism. Unfortunately, several other considerations need to be taken into account in the design of an HIV vaccine.

(i) Latency of the virus in infected cells: After introduction of the virus into the host, it may avoid the immune response by lying dormant inside the genome of cells which it infects until protective immunity subsides[17].

(ii) Potential for 'viral enhancement': Spread of the virus in the host may be facilitated by infection of Fc-bearing lymphoid cells (e.g. monocytes and macrophages) which phagocytose antibody coated virions[18].

(iii) Molecular mimicry of 'self' proteins by gp120: It has been proposed that the env protein may have structural similarities with MHC class II molecules, and hence the immune system may not have the capacity to recognize many of the epitopes of this antigen because of clonal deletion[17].

(iv) Ineffectiveness of humoral response in preventing HIV infection: Prince et al.[19] found that passive immunization of chimpanzees with the gamma-globulin fraction of seropositive individuals failed to protect them from subsequent HIV challenge. This is a particularly discouraging outcome since it indicates that the humoral response elicited is ineffective in the prevention of infection. However, these results may have been due to unforseen errors in experimental design. In a more recent study, these same investigators have reported a protective effect against a different strain of HIV[20].

Animal Models for Acquired Immunodeficiency Syndrome

In the development of a vaccine, suitable animal models are needed to investigate the disease process and to evaluate the efficacy of potential vaccines. One of the difficulties in research in AIDS and the development of an HIV vaccine is the lack of a good animal model, one in which HIV infects and induces an AIDS-like disease in a readily available laboratory animal. There are currently several models being used for AIDS research, and they can be divided into four categories in order of their increasing relevance to AIDS in humans: 1) retroviruses not related to HIV but which induce similar chronic diseases, 2) ungulate lentiviruses, 3) SIV of Old World primates, 4) HIV infection of chimpanzees.

1. Retroviruses Not Closely Related to HIV: Feline leukaemia virus (FeLV) is a type C retrovirus that produces a disease in cats which shares many features of AIDS. Infected animals develop profound immunosuppression, characterized by thymic atrophy, depletion of T lymphocytes, and prolonged allogeneic graft rejection times. The sequelae of this FeLV induced immunosuppression are similar to that seen in AIDS, including opportunistic infections, T and B cell lymphoma, and fibrosarcoma[21]. There are, however, numerous differences in the morphology and patho-

...ilarity between FeLV and HIV, and FeLV infection is not really an adequate model of AIDS. Nevertheless, this is an excellent model to screen potential inhibitors of reverse transcriptase which may be an important approach to the treatment of AIDS, and also to assess strategies in the development of retrovirus vaccine in a readily available laboratory animal[22].

2. Ungulate Lentiviruses: HIV is a member of the lentivirus subfamily. Morphologically HIV is virtually indistinguishable from other lentiviruses and biologically they share many similarities. All of these viruses have prolonged incubation periods, elicit weak antibody responses, and show extensive genetic mutation and antigenic drift. For these reasons, ungulate lentiviruses including maedi-visna virus of sheep, Caprine Arthritis-Encephalitis virus and Equine Infectious Anaemia virus, have received considerable attention in their relevance to human HIV infection. However, while HIV produces severe immunosuppression in its host, the ungulate lentiviruses produce only chronic inflammatory or degenerative diseases in the infected animals and are not oncogenic[23,24]. Moreover, the host animals are cumbersome to work with in a laboratory setting. At the present time, they are only considered as a useful model to study mechanisms of avoidance of host immune system and vaccination strategy[21].

3. Simian Immunosuppressive Viruses (SIV) of Old World Primates: This group of viruses was first isolated from rhesus monkeys[25] and subsequently in other old world primates. The virus produces in these primates a disease that remarkably parallels that of human AIDS. From six months to one year following inoculation with the virus, the animals develop lymphadenopathy syndrome, profound wasting, thymic atrophy, and crypto-sporidiosis[21]. The SIV/macaque system is thus an excellent model for the study of AIDS and for the testing of vaccine efficacy although it is nonetheless an imperfect one. SIV is not identical to HIV, and furthermore, the experimental animals are difficult to procure and are expensive.

4. HIV Infection of Chimpanzees: Chimpanzees and gibbons are the only animal species in which attempts at experimental infection with HIV have been successful. Following inoculation with the virus, consistent seroconversion has been observed, and HIV can be isolated from peripheral blood. The animals are thus clearly infected but up to the present time, no AIDS-like disease except for chronic infections has been observed even in animals infected by HIV-1 eight years ago[12]. While this is a true model of HIV infection, it remains to be shown whether the disease process is identical to that in humans. The first successful immunization against HIV-1 infection was reported in 1989[26], but due to the very limited availability of chimpanzees for experimental purposes, the model is not expected to be used for extensive vaccine testing.

New Insights on the Pathogenesis of HIV Infection

Several recent developments have made it necessary to question the validity of progress in the development of an HIV vaccine made in animal models. Two studies in particular have provided data which may alter our understanding of the role of HIV in AIDS. In a recent correspondence to the journal Nature, Stott[27] reports some curious results which were obtained in experiments involving macaque monkeys and SIV infection. It was found that vaccination of macaques with inactivated SIV-infected human T cells protected the animals from subsequent challenge with live virus presented in a similar fashion. However, the unexpected findings involved the fact that several of the 'control' animals (i.e. those "vaccinated" only with uninfected human T cells), also exhibited protective immunity against SIV challenge. Further experiments revealed that positive immunity resulted from a humoral response elicited against determinants on the transferred human T cells and this can be stimulated by either purified SIV or xenogenic T cells.

Similar results have also been published by Kion and Hoffmann[28] who used a mouse model to investigate HIV immunity. They found that production of antibodies against HIV antigens (gp120 and p24) could be induced in mice after inoculation with HIV-infected T lymphocytes obtained from another strain of mouse. Surprisingly, these antibodies were also detected in control groups who had only received uninfected allogenic T cells.

Proper interpretation of these data will require further investigations, but one explanation which has already been forwarded is that AIDS is actually an autoimmune disorder triggered by HIV infection[29]. Depletion of T helper cells in the affected individual is proposed to result from activation of autologous anti-class II MHC antibodies and/or cytotoxic T lymphocytes which are normally restrained by self-tolerance. This subpopulation is postulated to be stimulated into action by combined exposure to the viral gp120 antigen (which is believed to bear structural similarity to class II MHC molecules) and to foreign lymphocytes (expressing immunogenic class II MHC molecules). This response to foreign class II MHC and foreign class II MHC-like (gp120) molecules is thus proposed to result in reactivity against the host's own class II MHC bearing cells. The most important implication

of this hypothesis is that AIDS is postulated to be primarily an autoimmune disease which results in the destruction of CD4+ cells, rather than one arising from the continuous pathogenic effects of an infectious retrovirus. If these preliminary results are substantiated, the repercussions will undoubtedly be the focus of AIDS research for some time to come.

Experimental and Clinical Trials of Potential AIDS Vaccines

A variety of HIV vaccines are currently under development at several institutions and research centers. Information about the groups involved in this work, as well as the approaches and stages of development has been summarized in table 1.

As with any other vaccines, extensive clinical trials are required to establish the safety and efficacy of the vaccine before it can be used in the general public. Clinical trials are normally divided into three phases:

1. Phase 1: This is designed to determine whether or not the candidate vaccine preparation is safe or it elicits unanticipated adverse reactions. The test is normally done with a small number of healthy volunteer subjects.

2. Phase 2: This follows Phase 1 and is designed to determine the optimal dosage regimen with respect to safety and immunogenicity. A larger number of volunteers are recruited for this trial. Included in this group of volunteers will be persons at high risk for acquiring the specific (HIV-1) infection. The purpose is to determine whether or not this particular group of individuals to which the vaccine is mainly targeted, experiences any unusual reactions to the vaccine compared to the population in general.

3. Phase 3: The last phase of the clinical trial is designed to evaluate the capacity of the candidate vaccine to protect against disease. The trial should be a placebo controlled, randomized and double-blind test to generate unbiased information on the efficacy of the vaccine.

Clinical trials of HIV vaccines present unique technical difficulties and ethical issues. Some of the technical

Table 1: Summary of ongoing animal and clinical trials of HIV vaccines

Group	Molecular approach	Status of work
Applied Biotechnology, Inc.	Pseudovirion containing both core and envelope proteins; deletes infectious RNA - vaccinia carrier	animal trials
Oncogen (Bristol-Myers-Squibb Co.)	gp160 in vaccinia	in clinical trials since 1988
British Biotechnology Group	p24 in virus-like particle	phase I trials underway
Biocin (Chiron/CIBA-GEIGY)	p120 (unglycosylated)	clinical trial since 1989
Genentech, Inc.	gp120	animal clinical trials
Immune Response Corp.	radiation and chemically inactivated core proteins	phase III for immunotherapy
Cambridge Bioscience Corp.	gp160	private studies
Connaught Labratories, Ltd.	Pseudovirion containing both core and envelope proteins; deletes infectious RNA	animal trials
Microgenesys Inc.	p24, gp160	clinical trials with gp160 since 1987, with p24 since late 1990.
Molecular Vaccines	gp160	laboratory studies
Repligen Corp.	gp120	chimp trials
Viral Technologies, Inc.	p17	phase I trials since 1989

(modified from J. Cohen, AIDS vaccines conference: Is more better? Science 250 (4979):370 (1990))

difficulties have been discussed in previous sections. It is worth emphasizing that the best vaccine for a viral infection is a live attenuated vaccine which can provoke the full range of immune response. In the case of HIV infection, it is impossible to tell whether live attenuated HIV is safe or not before use, and such a vaccine is unlikely to be considered an acceptable risk.

In addition to the technical difficulties in developing an appropriate vaccine against HIV, the clinical trial of such a vaccine gives rise to certain ethical dilemmas. The first issue is that all individuals who receive the vaccine will become seropositive for antibody against HIV. While adequate certification from the agency conducting the trial can be issued and tests to distinguish between true HIV infection and immunization are available, the individual will still face the potential risk of social stigmatism and discrimination arising from being HIV positive when identified, for example, in a pre-employment screening test. Second, since AIDS is almost always a fatal disease and effective therapy for it is still unavailable, it would be unethical not to counsel individuals participating in the Phase 3 clinical trials about the necessity to avoid HIV exposure. Yet, if the participating individuals take the proper precautions to avoid contracting the disease, then the efficacy data needed to assess the vaccine may be biased. Finally, due to the lack of a suitable animal model, trials will necessarily be done in most cases in the absence of established evidence of protective efficacy from animal studies. This further complicates the other ethical issues already outlined.

Conclusions

The current epidemic of AIDS and the lethality of the disease mandates the rapid development of a vaccine against HIV. Although there are numerous technical hurdles to surmount and difficult ethical issues to consider, progress is slowly being made. The year 1989 has been considered a turning-point and clinical trials of potential HIV vaccines have begun in the U.S.[30] and in England. While results from many of these trials have not yet been published, there is guarded optimism that an effective HIV vaccine will be available within a few years[31]. However, recent data obtained from immunization studies in animal models may make it necessary for us to redefine our understanding of the fundamental pathogenic mechanisms involved in AIDS and hence the future role of an HIV vaccine.

References

1. Gottlieb, M.S., Schroff, R., Schanker, H.M., Weisman, J.D., Fan, P.T., Wolf, R.A. and Saxon, A. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N. Engl. J. Med., 5:1425-1431,1981.

2. Barre-Sinoussi, F., Chermann, J.C., Rey, F., Nugeyre, M.T., Chamaret, S., Gruest, J., Dauguet, C., Axler-Blin, C., Vezinet-Brun, F., Rouzioux, C., Rozenbaum, W. and Montagnier, L. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science, 220:868-871,1983.

3. Gallo, R.C., Sarin, P.S., Gelmann, E.P., Robert-Guroff, M., Richardson, E., Kalyanaraman, V.S., Mann, D., Sidhu, G.D., Stahl, R.E., Zolla-Pazner, S., Leibowitch, J. and Popovic, M. Isolation of human T-cell leukemia virus in acquired immune deficiency syndrome (AIDS). Science, 220:865-867,1983.

4. AIDS Update-1990, 3(28):6-8,1990.

5. Greene, W.C. The molecular biology of human immunodeficiency virus type I infection. N. Engl. J. Med., 324:8-317,1991.

6. Gelderblom, H.R., Ozel, M. and Pauli, G. Morphogenesis and morphology of HIV. Structure-function relations. Arch. Virol., 106:1-13,1989.

7. Hockley, D.J., Wood, R.D., Jacobs, J.P. and Garrett, A.J. Electron microscopy of human immunodeficiency virus. J. Gen. Virol., 69:2455-2469,1988.

8. Shin, D.W., Avers, J. In: AIDS/HIV Reference Guide for Medical Professionals. Center for Int. Immunology and Disease at UCLA, 1989, pp.1-28.

9. Dalgleish, A.G., Beverley, P.C., Clapham, P.R., Crawford, D.H., Greaves, M.F. and Weiss, R.A. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. Nature, 312:763-767,1984.

10. Redfield, R.R. and Burke, S.D. HIV infection: The clinical picture. Sci. Am., 259:90-98,1988.

11. Walker, B.D. Chakrabarti, S., Moss, B., Paradis, T.J., Flynn, T., Durno, A.G., Blumberg, R.S., Kaplan, J.C., Hirsch, M.S. and Schooley, R.T. HIV-specific cytotoxic T lymphocytes in seropositive individuals. Nature, 328:345-348,1987.

12. Koff, W.C. and Hoth, D.F. Development and testing of AIDS vaccines. Science, 241:426-432,1988.

13. Hosmalin, A., Clerici, M., Houghten, R., Pendleton, C.D., Flexner, C., Lucey, D.R., Moss, B., Germain, R.N., Shearer, G.M. and Berzofsky, J.A. An epitope in human immunodeficiency virus 1 reverse transcriptase recognized by both mouse and human cytotoxic T lymphocytes. Proc. Natl. Acad. Sci., 87:2344-2348,1990.

14. Hu, S. et al. Processing, assembly, and immunogenicity of HIV-1 core antigens expressed by recombinant vaccinia virus. In: Vaccines 90, p.231-236, Cold Spring Harbour Lab. Press, 1990.

15. Redfield, R.R. et al. A phase I evaluation of the safety and immunogenicity of vaccination with recombinant gp 160 in patients with early human immunodeficiency virus infection. N. Engl. J. Med. 324:1677-1684,1991.

16. Palker, T.J., Clark, M.E., Langlois, A.J., Matthews, T.J., Weinhold, K.J., Randall, R.R., Bolognesi, D.P. and Haynes, B.F.

Type-specific neutralization of the human immunodeficiency virus with antibodies to env-encoded synthetic peptides. Proc. Natl. Acad. Sci., 85:1932-1936,1988.

17. Zhou, E.M. and Kennedy, R.C. Strategies for developing vaccines against acquired immunodeficiency syndrome. Biochim. Biophys. Acta., 989:1-313,1989.

18. Takeda, A., Ennis, F.A. and Sweet, R.W. Model for enhancement of HIV-1 infection by antibody. In: Vaccines 90, p.333-337, Cold Spring Harbour Lab. Press, 1990.

19. Prince, A.M., Horowitz, B., Baker, L., Shulman, R.W., Ralph, H., Valinsky, J., Cundell, A., Brotman, B., Boehle, W., Rey, F., et al. Failure of a human immunodeficiency virus (HIV) immune globulin to protect chimpanzees against experimental challenge with HIV. Proc. Natl. Acad. Sci., 85:6944-6948,1988.

20. Prince, A.M. et al. Apparent prevention of HIV infection by HIV immunoglobulin given prior to low-dose HIV challenge. In: Vaccines 90, p.347-351, Cold Spring Harbour Lab. Press, 1990.

21. Desrosiers, R.C. and Letvin, N. Animal models for acquired immunodeficiency syndrome. Rev. Infect. Dis. 9:438-446, 1987.

22. Osterhaus, A., Weijer, K., Uytdenhaag, F., Jarrett, O., Sundquist, B. and Morein, B. Induction of protective immune response in cats by vaccination with feline leukemia virus iscom. J. Immunol. 135:591-596,1985.

23. Narayan, O. and Cork, L.C. Lentiviral diseases of sheep and goats: chronic pneumonia, leukoencephalomyelitis and arthritis. Rev. Infect. Dis., 7:89-98,1985.

24. Stephens, R.M., Casey, J.W. and Rice, N.R. Equine infectious anemia virus gag and pol genes: relatedness to visna and AIDS virus. Science, 231:589-594,1986.

25. Daniel, M.D., Letvin, N.L., King, N.W., Kannagi, M., Sehgal, P.K., Hunt, R.D., Kanki, P.J., Essex, M. and Desrosiers, R.C. Isolation of a T-cell tropic HTLV-III-like retrovirus from macaques. Science, 228:1201-1204,1985.

26. Berman, P.W., Gregory, T.J, Riddle, L., Nakamura, G.R., Champe, M.A., Porter, J.P., Wurm, F.M., Hershberg, R.D., Cobb, E.K. and Eichberg, J.W. Protection of chimpanzees from infection by HIV-1 after vaccination with recombinant glycoprotein gp120 but not gp160. Nature, 345:622-625,1990.

27. Stott, E.S. Anti-cell antibody in macaques Nature, 353:393,1991.

28. Kion, T.A. and Hoffmann, G.W. Anti-HIV and anti-anti MHC antibodies in alloimmune and autoimmune mice. Science, 253:1138-1140,1991.

29. Maddox, J. AIDS research turned upside down. Nature, 353:297,1991.

30. Ezzell, C. Trials of vaccine against AIDS to begin in humans. Nature, 328:747-747,1987.

31. Schild, G.C. and Minor, P.D. Modern vaccines. Human immunodeficiency virus and AIDS: challenges and progress. Lancet, 335:1081-1084,1990.

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Management of Prolactinomas: A Review

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LORETTA DE GROOT

Abstract

Prolactin secreting pituitary tumours are commonly occurring neoplasms which may present either with their hormonal effects or as space occupying lesions. The diagnosis is made both biochemically and through radiologic investigation of the pituitary gland.

Treatment is primarily medical, although surgery is useful in selected cases. The findings at radiologic follow-up leave many unanswered questions as to the mechanism of many of the demonstrated changes. Histologic features which account for the radiologic characteristics and recent developments in imaging modalities are discussed.

Tumours of the pituitary gland are commonly occurring neoplasms, comprising 10-15% of all intracranial tumours. Series of unselected postmortem examinations have demonstrated a 6-23% incidence of evidence of subclinical pituitary microadenomas (adenomas less than 10mm in diameter)[1].

Pituitary adenomas are highly variable in size; tumours greater than 10mm in diameter are referred to as macroadenomas. Most microadenomas do not progress to become macroadenomas; micro and macroadenomas are indeed separate entities each having a different natural history.

The majority of pituitary tumours are benign, slow growing and secrete one or more hormones. The most common functional pituitary tumours are those which secrete prolactin. Prolactin secretion by the anterior pituitary under normal circumstances is controlled by the hypothalamus. The inhibitory factor arising from the arcuate nucleus, is dopamine. Whether formation of prolactinomas is due to an intrinsic abnormality in the anterior pituitary or is related to chronic loss of dopamine control from the hypothalamus remains largely unclear.

Clinical Features

The usual clinical manifestations of prolactinomas are gonadal dysfunction, mass effect of the lesion, and more rarely, hemorrhage into large tumours. Hyperprolactinemia causes gonadal dysfunction by acting at the

level of the hypothalamus; prolactin physiologically inhibits the release of luteinizing hormone releasing hormone (LHRH) thus resulting in decreased levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH). The symptoms of amenorrhea, infertility and decreased libido are a result of decreased gonadal stimulation while galactorrhea is a direct result of hyperprolactinemia. The fact that the observed incidence of microprolactinomas is three times higher in females than males is attributed to more frequent inattention to symptoms in males[2].

Macroprolactinomas, like any other pituitary tumour, may cause symptoms because of mass effect. Visual field abnormalities are related to the optic chiasm's close proximity to the pituitary gland, lying anterosuperior to the gland. Bitemporal hemianopia is a classic sign; bitemporal scotomas are often observed, but nine percent of cases involve only the visual field of a single eye[3].

Tumours that extend laterally into the cavernous sinus may cause palsies of the nerves innervating the extraocular muscles. The third cranial nerve is most commonly affected and the lesion is often pupil sparing. Headaches also occur commonly in patients with prolactinomas.

Macroprolactinomas may rarely present as pituitary apoplexy, a massive bleed into a tumour which causes pituitary infarction. Findings may include ophthalmoplegia, visual disturbances, and panhypopituitarism as a result of direct pressure of the mass on the normal pituitary tissue. The resultant destruction of the pituitary gland and tumour may result in normalization of the hyperprolactinemia. The findings may develop over the course of 24-48 hours or may present as sudden death. Pituitary apoplexy is a neurosurgical emergency.

Investigations

The differential diagnosis of hyperprolactinemia in addition to prolactinoma, includes drug induced (ie. drugs that interfere with normal dopamine metabolism), hyperestrogen state (i.e. pregnancy) and renal failure. Lesions in, or near, the hypothalamus including tumours, infections, sarcoidosis, or vascular abnormalities are associated with elevated prolactin levels and must be ruled out.

Serum prolactin levels greater than 300ng mL^{-1} (greater than 100ng mL^{-1} in the proven non-pregnant patient) are diagnostic of prolactinoma.

Radiologic Investigation

Sella tomography is not a useful screening test for prolactinomas. Prior to the use of computed tomography, many minor variants in normal anatomy were uncritically accepted as evidence of pituitary abnormality. In the late 1970's, double blind evaluations using proper controls cast doubt on the contribution of conventional radiographs[4].

Currently, problems arise in providing a pathologically verified estimate of the false negative rate for computed tomography as few patients with hyperprolactinemia and negative radiologic findings will be candidates for surgery or postmortem examination.

Coronal cross-sectional images are the preferred method of investigation[4], as they demonstrate asymmetry of internal architecture, surface contours, and relationship of tumour to normal tissue. Coronal sections demonstrate the gland's upper contours better than do axial sections.

Macroadenomas may enlarge the sella, invade the sphenoid sinus, displace the carotid sinus or encroach on the optic chiasm. Microadenomas generally do not enlarge the sella nor produce significant mass effect. On unenhanced CT, prolactinomas appear at a density slightly less than that of normal pituitary gland or cavernous sinus. It is very unusual to see bony destruction or calcifications except for small flecks in the capsule.

There is a triad of findings which suggest the presence of prolactinomas: hypodense region within the gland, convex upper surface of the gland, and a gland height greater than 9mm. On T_1-weighted magnetic resonance (MR) images, signal intensity of an adenoma is lower than that of brain.

The utility of MR imaging has progressed rapidly from the early 1980's when resolution was not high enough for the diagnosis of microadenomas. By the mid 1980's it was predicted that MR would surpass CT in diagnostic sensitivity[5], and by 1988 a series had been published which demonstrated MR to be more sensitive than CT for determining the presence of cystic degeneration, small hemorrhages and small adenomas[6]. Paramagnetic intravenous contrast agents such as gadolinium-DTPA have been shown to add diagnostic specificity in selected circumstances[7]. As postmortem series have demonstrated a high incidence of pituitary microadenomas, it is not unexpected that 20% of normal persons have microadenoma-like areas demonstrable on MR imaging. Thus, armed with an incomplete knowledge of the natural history of untreated microprolactinomas, this group may be treated unnecessarily.

Positron emission tomography (PET) scanning, though hampered by poor resolution, may decrease the number of false positive results when used in conjunction with MR imaging[8]. In one series, 20 patients with documented

adenomas were PET scanned with similar sensitivity and specificity as CT/MR[8].

The MR signal changes seen in patients with bromocriptine treated prolactinomas are diverse and at this time they cannot be related to specific histologic changes. In the future, however, this modality may serve as a guide for further classification[9].

Treatment

Objectives of treatment include suppression of hormone secretion, reduction of tumour mass, normalization of cranial nerve function, maintenance or restoration of anterior pituitary function and prevention of disease progression[10]. Options for management include observation, medication, surgery or radiation.

The decision simply to observe a patient with moderate hyperprolactinemia in the absence of a demonstrated tumour is somewhat controversial even if a patient is not concerned about the hypogonadal symptoms. Osteoporosis is a significant complication of hyperprolactinemia, where circulating levels of estradiol and testosterone are reduced, leading to reduction in bone density. An argument can be made that hypogonadism due to hyperprolactinemia is a firm indication for therapy, even when there is no risk of tumour expansion, nor a preference for improved sexual function. However, it is the general consensus that not all patients with microprolactinomas require treatment[3].

The major drugs used in treatment of prolactinomas are the dopamine agonists. Bromocriptine, a dopamine agonist, has been found to correct hyperprolactinemia due to prolactinoma in 90% of cases and decreases tumour size in 70-80% of cases. The resistant cases that occur are thought to be a result of a dopamine receptor defect or a defect in second messenger (cyclic AMP) metabolism in the tumour cell population[11].

The mechanism whereby bromocriptine reduces tumour size can be established by histologic examination of pituitary tissue that has been transphenoidally resected following pre-operative bromocriptine therapy. After short term therapy (i.e. less than two weeks) there is an accumulation of secretory granules, the result of decreased exocytosis. There is also evidence of decreased protein metabolism; there is decreased cytoplasmic volume and the number of ribosomes, endoplasmic reticulum and Golgi bodies are reduced. Chromatin becomes clumped and inactive in appearance. Cellular necrosis and fibrosis are also seen[12]. PET studies have demonstrated that amino acid metabolism is decreased by 40% within two to four hours of intravenous bromocriptine therapy initiation[13]. It is unclear whether the decrease in protein metabolism is a result of inhibition by increased intracellular bromocriptine granules or whether it is due to a more direct effect of the bromocriptine.

The decrease in tumour volume is often striking. In one recent series of 27 patients, 12 patients had a greater than 50% decrease in volume over three months of therapy, and all of the patients had at least some demonstrable decrease in mass[14]. Other series report similar results with only infrequent reports of patients who had a hormonal response (i.e. a normalization of prolactin levels) with no change in tumour size[15]. All series have demonstrated that there is no correlation between prolactin response and tumour volume response. In the earlier series, failure to demonstrate tumour shrinkage could be related to low resolution of early generation imaging equipment.

One series of patients had two prolactinomas that actually grew in size despite the lowering of measured prolactin levels while on bromocriptine therapy[16]. In these patients, compliance was questioned on clinical grounds. It is known that intermittent bromocriptine use will have no effect on tumour size, but will suppress prolactin levels if ingested prior to a blood sample being taken[17].

When tumour mass size reponds to bromocriptine the response is often within 72 hours of onset of therapy. This rapid decrease in size has lead several investigators to advocate the use of bromocriptine as first line therapy for patients with macroprolactinomas when shrinkage is urgently required. As well, chiasmal compression is not necessarily an emergency situation, and a better result will often be attained if bromocriptine is administered in place of immediate transphenoidal surgery[15].

If there is no urgency in effecting shrinkage, three months is an adequate trial of bromocriptine before surgery[14]. A preoperative course of bromocriptine tends to improve efficacy of surgery by shrinking the tumour mass to be resected.

Commonly occurring side effects of bromocriptine therapy include nausea, gastric irritation, postural hypotension and headache. These side effects usually resolve within several weeks of the onset of therapy. Bromocriptine therapy must be continued indefinitely as tumours will recur if the therapy is discontinued. In the case of very large tumours rapid shrinkage may cause hemorrhage or cerebral spinal fluid (CSF) rhinorrhea.

MR studies suggest that intratumor microbleeding may be a common side effect in up to 30% of patients treated with bromocriptine. This microbleeding may be the cause of the headache that is so often seen in these treated patients. A recent series of 68 MR studies of patients with bromocriptine treated prolactinomas demonstrated 18 patients with evidence of hemorrhage based on T_1-weighted image signal intensity. Of these 18 patients, five

eventually needed transphenoidal resection and had histologically proven hemorrhage[19]. Other histologic series, however, do not support this figure of 30% hemorrhage prevalence[12].

Transphenoidal resection of prolactinomas is now performed on only a small proportion of patients. Operative treatment provides the opportunity for rapid decompression. However, when surgery is used to relieve optic chiasm or other cranial nerve compression, it only uncommonly results in a restoration of function due to the difficult operative conditions involved in such a tumour. Surgical therapy is also associated with a very high relapse rate with both tumour recurrence and increased prolactin levels occurring in 20-80% of patients five years postoperatively.

The best success rate (20% recurrence) is observed in patients with microadenomas with prolactin levels less than 250ng mL^{-1}. Surgery can itself have significant side effects such as CSF rhinorrhea (3.3%), permanent visual loss (1.5%), oculomotor palsy (0.6%) and meningitis (0.5%).

The current balance of evidence suggest that surgery should only be considered after a failed trial of bromocriptine therapy.

Summary

The approach to hyperprolactinemia requires that one be alert to the fact there are several different possible etiologies. Once the diagnosis of prolactinoma is in hand, there is effective medical therapy. Surgical therapy may be considered as well. The radiologic follow-up of treated prolactinomas poses new questions about the assesment of the mechanism of response at the cellular level and leaves unanswered questions as to the significance of certain MR imaging findings.

References

1. Burrow GM, Wortzman G, Prowcastle WB, et al. Micro-adenomas of the pituitary and abnormal sellar tomograms in an unselected autopsy series. N Eng J Med 1981; 304:156-158.

2. Rodman EF, Goodman R. Prolactinomas in males. p 115 In Olefsky JM, Robbins RJ (eds). Prolactinomas: Churchill Livingstone, New York, 1986.

3. Daniels GH, Martin JB. Neuro-endocrine regulation and diseases of the anterior pituitary and hypothalamus. p 1671 In Braunwald D, et al. (eds) Harrison's principles of Internal Medicine: McGraw Hill, Toronto, 1991.

4. Hendriks MJ. Computed tomography of the pituitary gland. p 3. Van Gorcum, Assen, Netherlands, 1988.

5. Kulkarni MV, Lee KF, McArdle CB, et al. 1.5-T MR imaging of pituitary microadenomas: technical considerations and CT correlation. AJNR 1988;9:5-11.

6. Mikhael MA, Ciric IS. MR imaging of pituitary tumours before and after surgical and/or medical treatment. JCAT 1988;12:441-445.

7. Stadnik T, Stevenaert A, Beckers A, et al. Pituitary micro-adenomas: diagnosis with two and three dimensional MR imaging at 1.5T before and after injection with gadolinium. Radiology 1990;176:419-428.

8. DeSouza B, Brunetti A, Fulham MJ, et al. Pituitary micro-adenomas: a PET study. Radiology 1990; 177:39-44.

9. Weissbuch SS. Explanation and implications of MR signal changes within pituitary adenomas after bromocriptine therapy. AJNR 1986;7:214-216.

10. Vance ML, Thorner MO. Prolactin: hyperpro-lactinemic syndromes and management. p 408-419 In DeGroot J (ed). Endocrinology: Saunders, New York, 1989.

11. Pellegrini I, Rasolonjanahary R, Gunz G, et al. Resistance to Bromocriptine in prolactinomas. J. Clin. Endoc. and Metab 1989;69:500-509.

12. Hiroshi M, Shintaro M, Youichi S, et al. Effects of bromocriptine on prolactin-secreting pituitary adenomas. Cancer 1985;56:230-238.

13. Bergstrom M, Muhr C, Lundberg PO, et al. Rapid decrease in amino acid metabolism in prolactin-secreting pituitary adenomas after bromocriptine treatment: A PET study. JCAT 1987;11:815-819.

14. Molitch ME, Elton RL, Blackwell RE, et al. Bromocriptine as primary therapy for prolactin-secreting macroadenomas: Results of a prospective multicentre study. J Clin Endoc Metab 1985;60:698-705.

15. Schettini G, Lombardi G, Merola B, et al. Rapid and long lasting suppression of prolactin secretion and shrinkage of prolactinomas after injection of long-acting repeatable form of bromocriptine (parlodel lar). Clin Endoc 1990;33:161-169.

16. Kupersmith MJ, Kleinberg D, Warren FA, et al. Growth of prolactinoma despite lowering of serum prolactin by bromocriptine. Neurosurgery 1989;24:417-423.

17. Vance ML, Evans WS, Thorner OT. Bromocriptine. Annals of Internal Medicine 1984;100:78-91

18. Lesser RL, Zheutlin JD, Boghen D, et al. Visual function improvement in patients with macroprolactinomas treated with bromocriptine. Am Journ Ophthalmology 1990;109:535-543.

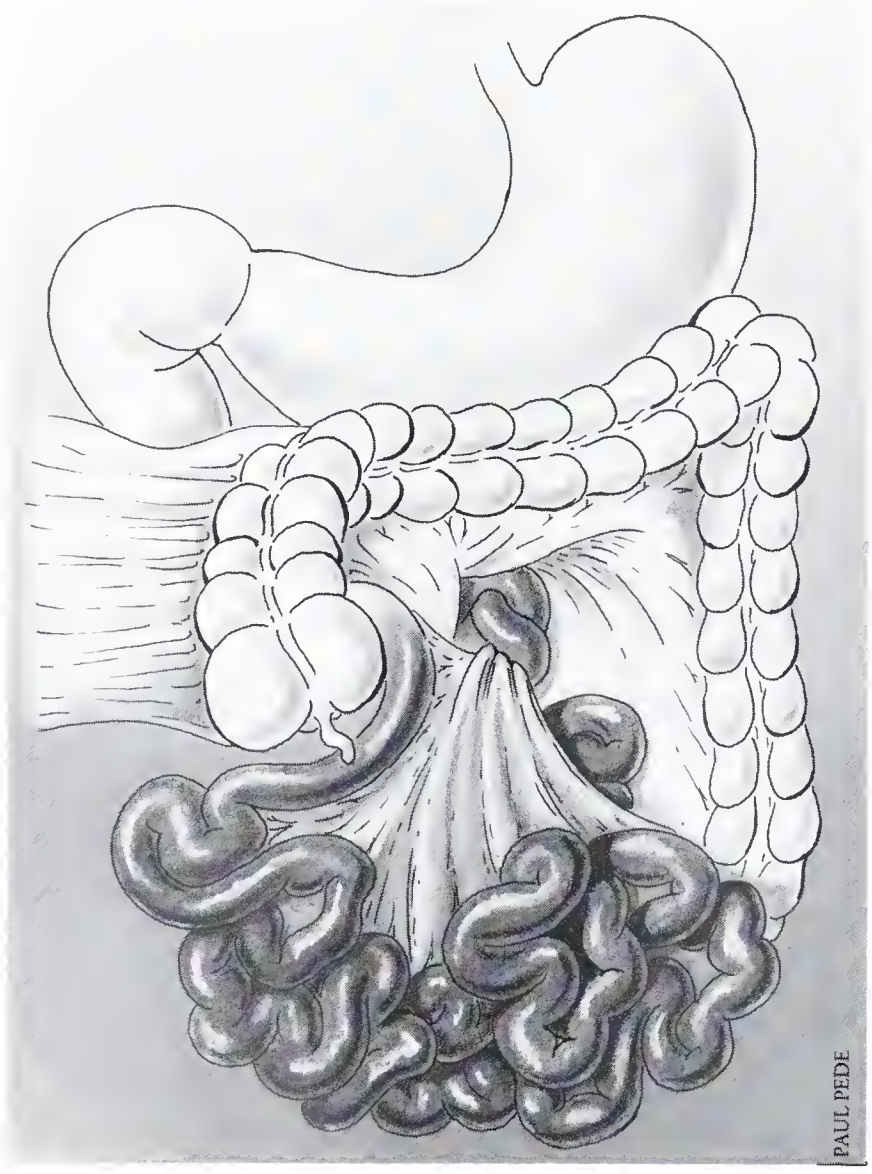
19. Yousem DM, Arrington JA, Zinreich SJ, et al. Pituitary adenomas: possible role of bromocriptine in intratumoral hemorrhage. Radiology 1989; 170:239-243.

Intestinal Volvulus Presenting as Acute Pancreatitis

Ken J. Berger, 9T2

Abstract

A common complaint in the pediatric age group is abdominal pain. There is a large differential diagnosis for this complaint which varies according to the age of the child. The initial challenge for the physician is deciding whether or not a surgical abdomen is present. Misdiagnosis of surgically treatable conditions in children often leads to significant morbidity and mortality. The following case highlights malrotation with midgut volvulus, which is one of the more important, commonly misdiagnosed, conditions leading to abdominal pain in the pediatric population. The case discusses a two-year-old child who was misdiagnosed as having acute pancreatitis until such time as a deterioration in his condition led to a laparotomy revealing gangrenous bowel. The goal of the present paper is to make physicians who deal with children aware of this condition. It is important to emphasize that an organic etiology - especially one with a clear surgical intervention such as midgut volvulus - must be excluded first from any differential diagnosis of abdominal pain in children. The ultimate challenge is to diagnose and surgically treat intestinal volvulus before the intestine becomes gangrenous. An accurate diagnosis may reduce the incidence of both short bowel syndrome and death from sepsis following intestinal volvulus.



Introduction

Malrotation of the intestine is defined as a failure of the normal 270 degree counterclockwise rotation of the gut in utero. This causes a malfixation of the mesentery resulting in the threat of volvulus. Midgut volvulus is defined as a twisting of the intestine upon its vascular pedicle. This may cause intestinal obstruction, intestinal vascular compromise or both.

Malrotation with midgut vovulus is common. Most patients with the condition (70%) present with symptoms in the first month of life[1]. There are conditions which mimic malrotation of the gut with volvulus, but these conditions vary with the age of the pediatric patient. In infancy, conditions mimicking malrotation are often other congenital causes of intestinal obstruction. In the older age groups, malrotation is more likely mimicked by causes of recurrent abdominal such as; appendicitis, kidney problems, lactose intolerance, porphyrias, sickle cell disease, and psychogenic abdominal pain. Psychogenic abdominal pain is only a diagnosis of exclusion. It is, however, more common in girls over five years of age who complain of vague periumbilical pain with no associated symptoms or signs[2]. This paper describes a case of acute pancreatitis mimicking malrotation of the intestine with midgut volvulus leading to intestinal gangrene and sepsis. A life saving operation

was required when the patient deteriorated - necessitating the removal of almost all of the small intestine and resulting in short bowel syndrome.

Presentation of Case

A two-year-old male was transferred by air ambulance to the Hospital for Sick Children (HSC) from Port Arthur General Hospital in Thunder Bay. He presented with a two-day history of severe crampy epigastric abdominal pain and 12 episodes of bilious vomiting.

The day prior to transfer, he presented to the emergency department pale, diaphoretic and listless. He had not had a bowel movement in two days. On inquiry, he had a three-month history of diarrhea and three episodes of severe vomiting leading to dehydration requiring hospitalization and fluid resuscitation. No diagnosis was made at this time. Also during this period, the child's stool was watery, soft and yellow with four bowel movements per day. He was measured to be below the third percentile in weight, but normal in height and head circumference. He was on no known medications and had no previous history of trauma or other relevant past medical illness.

On the day prior to transfer his condition began to deteriorate. He became bradycardic and hypotensive. He had a cardiac arrest with a period of asystole lasting five minutes and developed seizures. Consequently, he was intubated, ventilated and given fluid boluses containing solucortef, dopamine, ampicillin, gentamicin, calcium carbonate and phenobarbital by infusion. His condition eventually stabilized at critical, and he was transfered to the Intensive Care Unit at HSC.

On physical examination, the patient had a decreased level of consciousness. His pupils were equal and reactive to light. There was no neck stiffness. On inspection, his abdomen showed an increased girth with bluish discoloration in the flank and periumbilical regions (Grey Turner's and Cullen's Sign). There were decreased bowel sounds, no organomegaly, and the abdomen was dull on percussion. His temperature was 38 degrees celsius, heart rate 200/min, blood pressure 88/58 mmHg and his respiratory rate was 60/min.

Initial lab results were: Urea nitrogen 14.7* mmol/L; creatinine 62 mmol/L; calcium 1.77* mmol/L; sodium 142 mmol/L; potassium 6.5* mmol/L; chloride 99 mmol/L; glucose 8.6* mmol/L; albumin 38 g/L; hemoglobin 100* g/L; PT 20.7* sec; PTT 53.4* sec; bilirubin < 18 micromol/L, AST 1339* IU/L, ALT 462* IU/L, ALP 85 IU/L, GGT not available and serum amylase 2,000* IU/L (* denotes abnormal lab value).

Course In Hospital

After one week the child failed to show any signs of clinical improvement. Copious amounts of foul smelling greenish fluid were removed from the peritoneal cavity via a Jackson-Pratt drain - a drain used to collect free fluid. The child's fever rose to 40.2 degrees celsius. His condition became very critical. He was thought to have developed septic shock.

A diagnostic laparotomy was performed at this time. It was suspected the patient had intra-abdominal sepsis. The diagnosis of malrotation and midgut volvulus with gangrenous small intestine was made. After counterclockwise reduction, necrotic bowel was resected from four cm beyond the ligament of Trietz to within two cm of the ileocecal valve. The definitive procedure was a jejunostomy and division of Ladd's Bands (Fig 1).

To prevent future difficulties diagnosing appendicitis it was decided an appendectomy be performed. Furthermore, a central venous line was placed to allow total parenteral nutrition.

The patient gradually improved and two weeks later the jejunostomy was closed. The remaining viable bowel was re-anastomosed, and the cecum was placed in the left upper quadrant to avoid the return of adhesions across the duodenum[3]. Finally, a gastrostomy was performed to allow G-tube feedings.

None of the common postoperative complications such as wound infection, bowel obstruction due to adhesive bands, or intussusception[4], occured in this child. His azotemia worsened, however, and he required hemodialysis. The pathologic diagnosis was acute ischemic hemorrhagic necrosis with focal perforation of the bowel.

Discussion

The child's acute presentation of epigastric pain and vomiting associated with signs suggestive of intra- and retroperitoneal hemorrhage, a high serum amylase and a low serum calcium, were thought to be consistent with acute hemorrhagic pancreatitis. The child's deterioration was thought to be due to shock secondary to blood loss, sepsis or possibly to a circulating factor which in severe pancreatitis causes myocardial depression[5].

The development of seizures was most likely secondary to anoxia and hypovolemia, although an electrolyte disturbance may have also contributed. The child's development of azotemia was probably due to a prerenal cause such as hypovolemia. An acute tubular necrosis, however, would have to be excluded by urinalysis. The hyperkalemia was most likely caused by an acute acidemia secondary to bilious vomiting. The elevated

AST and ALT levels were thought to be consistent with severe pancreatitis leading to an acute shock state with possible ischemic damage to the liver.

According to Weizman and Durie (1988)[6] the possible etiologies of acute pancreatitis in childhood include: viral infection (mumps, hepatitis B virus and Coxsackie viruses), trauma, anatomical abnormalities of the biliarypancreatic tree (choledochal cyst, stenosis and stricture), toxins (drugs), metabolic defects (cystic fibrosis and hyperlipidemia), hereditary or systemic diseases (Kawasaki's disease, inflammatory bowel disease, Reye syndrome and hemolytic uremic syndrome).[6]

In this case, midgut volvulus was mistaken for acute pancreatitis. It was only after laparotomy that the diagnosis was made. In retrospect, following analysis of both the history and physical examination, midgut volvulus should have been considered earlier in the child's course of illness. The past history of severe vomiting may have been due to intermittent volvulus, or intermittent compression of the third part of the duodenum by peritoneal (Ladd's) bands. The past history of diarrhea may have been due to mild twisting, leading to lymphatic obstruction with subsequent intestinal malabsorption and failure to thrive[1].

Since the mechanical obstruction of midgut volvulus is distal to the papilla of Vater, bilious vomiting would be a symptom consistent with this diagnosis. On physical examination, the abdominal distension is a clue to vascular compromise of the intestine, as it is unlikely for obstruction of the third part of the duodenum to cause abdominal distension alone. Midgut volvulus may also present as recurrent abdominal pain, chylous ascites, or - in the late stage of ischemia - red currant jelly stool[1].

As described by Schwartz et al (1989)[7], the midgut develops outside the abdomen and returns to the peritoneum around the tenth week of gestation where it then rotates counterclockwise 270 degrees and is fixed by its mesentary to the posterior abdominal wall (Fig 2). A malrotation is caused by a failure of this rotation. In a malrotation, the entire midgut is suspended on a narrow fulcrum consisting of the superior mesenteric artery and vein which may twist resulting in a volvulus and small bowel obstruction followed by midgut ischemia and necrosis (Fig 3).

The majority of cases of midgut volvulus present in the first year of life[4]. Other common causes of bowel obstruction in the pediatric age group include: Hirschsprung's disease; meconium ileus; meconium plug

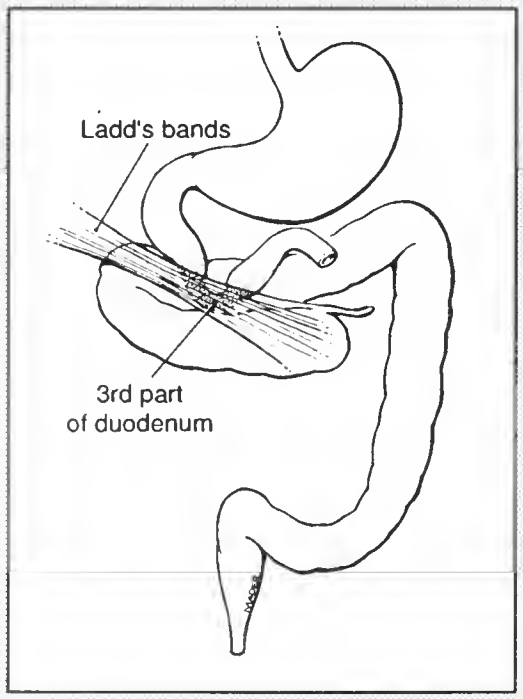


Figure 1. Ladd's Bands originate from the malpositioned cecum and usually attach to the right lateral peritoneal wall. They may cause mechanical obstruction at the third part of the duodenum.

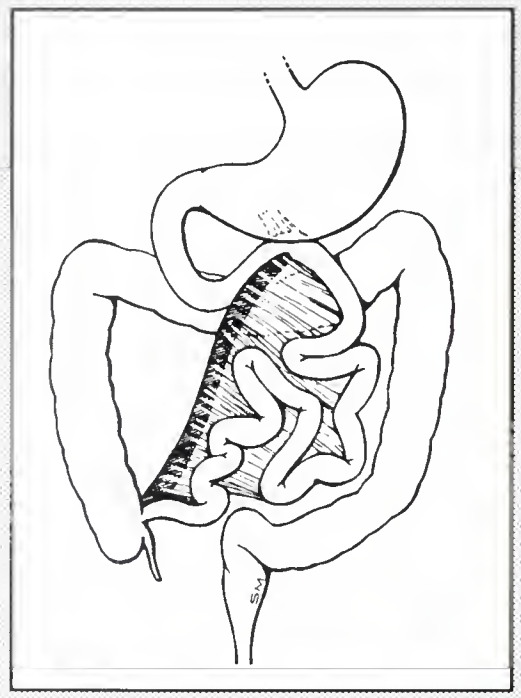


Figure 2. The Normal small bowel mesenteric attachment. The attachment of the mesentery extends from the ligament of Treitz to the ileocecal valve.

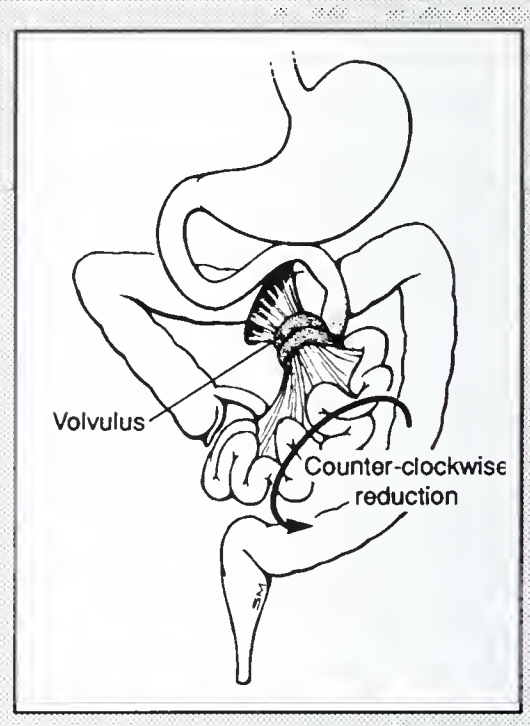


Figure 3. Abnormal small bowel mesenteric attachment. The resultant attachment is abnormally short, more readily permitting volvulus of the intestine. Volvulus of the intestine is corrected by counterclockwise reduction.

syndrome; pyloric stenosis; duodenal atresia and duplication of the alimentary tract[4].

Frazee et al studied intestinal volvulus in adults at the Mayo Clinic and found it was responsible for 5.7 % of small bowel obstructions (others causes of obstruction included adhesions 59%, malignancy 16.3% and hernia 15%)[8]. The researchers found volvulus was often associated with either a long mobile mesentery or the consumption of high fibre meals after prolonged intervals of fasting (as occurs during the 30-day fast of Ramadan after which Afghani Moslems demonstrate a higher incidence of intestinal volvulus)[8]. Neilson (1990)[9] found an association between volvulus and diverticulosis while Walker (1989)[10] found an association between volvulus and enteroenterostomy. Ashworth (1988),[11] in a study of four infant stillbirths in whom autopsy demonstrated intestinal volvulus, suggests meconium may act as a bolus causing the volvulus.

There is radiological evidence which may raise suspicion of malrotation. This includes a high and abnormally mobile cecum on barium enema (Fig 4), or an abnormal position of the ligament of Trietz on barium swallow (Fig 5)[4]. A volvulus may be suspected if there is a corkscrew appearance of the small bowel. Air-fluid levels provide evidence of small bowel obstruction, while gas in the portal vein provides evidence of a gangrenous gut.

Resecting a gangrenous bowel secondary to volvulus results in a condition known as the short bowel syndrome. Features associated with short bowel syndrome include; malnutrition, diarrhea, and failure to thrive[12]. Future development of small intestinal transplantation may prevent the morbidity and mortality associated with short bowel syndrome.

Conclusion

The mortality rate of gangrenous bowel secondary to an intestinal volvulus is 47%[13]. Early operative intervention should be performed to prevent ischemic bowel. A few hours may mean the difference between a reversible condition and the loss of most of the intestine. This paper illustrates the challenge faced by clinicians confronting abdominal pain in children. The best approach is a humble one using many resources including serial physical examinations, early surgical consultation, and appropriate use of investigations. The diagnosis and treatment of a surgically correctable condition is rewarding. Misdiagnosis and failure to treat is a real tragedy, particularly in the pediatric population.

Addendum

The child recovered and is now a four-year-old with short bowel syndrome. He is planning to begin junior-kindergarten in September, 1991. Presently, he is feeding by mouth and his diet is supplemented with G-tube feeding in the evening and B12 injections. He is presently above the 50th percentile for both height and weight.

Figure 4. Barium Enema of a high abnormally placed cecum suggestive of malrotation.

Figure 5. UGI showing an abnormal position of the ligament of Treitz suggestive of malrotation.

His most recent admission to HSC was for a hypokalemic metabolic acidosis, a complication of short bowel syndrome.

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References

1. Hilton S.V.W., Edwards D.K., and Hilton J.W., Practical Pediatric Radiology. W.B Saunders Company, Philadelphia, 1984:229-247.

2. Raffensperger J.G., Swenson's Pediatric Surgery 4th Edition. Appleton-Century-Crofts, New York, 1980:801-803

3. Swenson, O., Swenson's Pediatric Surgery 3rd Edition. Meridith Publishing Company, New York, 1969:614-618

4. Welch K.J., Paediatric Surgery 4th Edition. Medical Publishing Inc., Chicago:886-894

5. Way L.W., Current Surgical Diagnosis and Treatment 9th Edition. Appleton Lange. 1991:560-575

6. Weizman Z. and Durie P., Acute pancreatitis in Childhood. Journal of Paediatrics 1988:113:24-29

7. Schwartz S.I., Shires G.T. and Spencer F.C., Principles of Surgery 5 th Edition. McGraw-Hill Book Company, New York 1989:1702-1703

8. Frazee R.C., Mucha P., Farnell M.B., and Van Heerden J.A., Volvulus of the Small Intestine. Annals of Surgery 1988:565-568

9. Neilson D., Wilkinson N., and Magell J., Case of simultaneous diverticulosis , lipamatosis and volvulus of the small intestine. British Journal of Surgery 1990:77:105

10. Walker A.J., Small bowel vovulus secondary to entero-enterostomy for jejunal atresia. Journal of Paediatric Surgery 1989:24:1162

11. Ashworth T.G., Fetal volvulus of the small intestine. Journal of Clinical Pathology 1988:41:594-597

12. Filston H.C., Surgical Problems in Children Recognition and Referral. C.V. Mosby Company, St. Louis, 1982:24-28

13. Anderson J.R. and Welch G.H., Volvulus of the Small Intestine in Adults. World Journal of Surgery 1986:10:496-500

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The Delayed Effects of Ionizing Radiation to the Head and Neck

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Abstract

The potentially harmful effects of ionizing radiation have been recognized since the turn of the century. Ionizing radiation interacts with DNA causing chromosomal damage which, if left unrepaired, may lead to neoplasia. There exists today a large number of patients with a positive history for radiation exposure to the head and neck region presenting with some form of head and neck disease. This article discusses certain aspects of the history of radiation, the effects of ionizing radiation on the cell, radiogenic diseases affecting the head and neck area, treatment considerations and prophylactic measures. In addition, four illustrative cases evaluated during a summer student fellowship are presented.

Introduction

Knowledge of the harmful effects of ionizing radiation has been growing since the turn of the century. The potential for damage to cellular DNA along with subsequent tumor development is well documented[1-5]. Nonetheless, there are still many individuals who received radiation treatment decades ago (many for "benign" conditions such as acne, facial hirsutism, and tinea capitis) when the potentially harmful effects were not fully appreciated. Even with current guidelines, people continue to be exposed to radiation from occupational sources or from scatter secondary to cancer radiotherapy. Structures in the head and neck area have been found to be particularly vulnerable to radiation tumorigenesis[6]. Although the delayed effects of ionizing radiation to the head and neck have been well documented, the clinical recognition of these patients remains under-appreciated.

Historical Aspects: The untoward effects of radiation were first documented soon after the discovery of X-rays in 1895 by Roentgen and radioactivity in 1898 by Becquerel[7]. In 1928, the International Commission on Radiological Protection was formed in response to the many deaths occurring among radiologists. A study published in 1931 described the high incidence of bone and sinus tumours in radium dial workers[7]. However, appreciation of the need for radiation protection developed slowly. Benign skin conditions in the head and neck area continued to be treated by superficial radiation. There were no legal restraints on the use of X-ray machines in most countries - fluoroscopy for shoe fitting and therapeutic use in facial hair removal were widespread[8,9].

Following the nuclear bombing of Hiroshima and Nagasaki in 1945 and the early evidence of leukemia in survivors, the adverse effects of radiation were dramatically brought to public attention. A 1950 study performed by Duffy and Fitzgerald, was the first of many studies pointing to irradiation of the head and neck during childhood as an etiologic factor in thyroid gland neoplasia[6]. It became clear, at this point, that low-dose radiation had the potential for serious sequelae.

Effects of Radiation on Cells: Ionizing radiation (including X-rays and gamma rays) passes energy to

electrons, ejecting them from their orbits. If released from its atom, the ejected electron can cause biologic effects through excitations and ionizations in molecules of tissue[2]. The electron can excite and ionize cell macromolecules (eg. DNA) by direct interaction. In addition, the electron can act indirectly by ionizing the water molecule, generating a highly reactive free radical which is capable of interacting with DNA. Both of these mechanisms can cause cell damage[2].

The dose-response relationship of ionizing radiation has not been completely defined. There appears to be a balance between an increase in the proportion of cells that are transformed and a decrease in the proportion of cells that survive with increasing dose[4]. High-dose radiation is utilized in therapeutic cancer treatment to kill cancer cells. However, low-dose radiation from many sources (including possible scatter from cancer radiotherapy) damages DNA without cell death and is capable of carcinogenesis. Cancer risks associated with low-level irradiation can only be estimated using extrapolations from high-dose data, based on assumptions about the pertinent dose-response relationships and underlying mechanisms of carcinogenesis[4].

Carcinogenesis is a multistage process[1-5]. The first stage (initiation) is rapid and consists of irreversible genetic alterations[1]. While ionizing radiation is a relatively poor inducer of point mutations, it is an efficient inducer of gross chromosomal changes[3]. Ionizing radiation can cause single strand breaks, double strand breaks, base damage, base loss, denatured zones, intramolecular cross-links, and DNA-protein cross-links. Radiation may initiate lesions or localized change which lead to illegitimate reunions. Repair processes can be damaged, resulting in the persistence of chromosomal damage. There is some evidence of specific proto-oncogenes[2] that are activated after exposure to radiation (eg. K-ras, myc). As well, there is evidence of mutations in tumour suppressor genes caused by radiation. These changes appear to increase in a dose-dependent manner following exposure to ionizing radiation[4].

The second stage (promotion) is much slower than initiation and is not well understood[1]. It requires sustained exposure of the initiated cell to a promoter which usually acts via a hormone-like mechanism. Clonal populations of initiated cells are expanded. Promotion is reversible up to the development of the first autonomous tumour cell. Oncogenes which are present in the genomes of a variety of tumour cells can act as permissive or protective factors in the carcinogenic process[5].

The final stage (progression) consists of the sequence of changes through which successive alterations in neoplastic cells give rise to autonomous clonal derivatives[1]. Progression to malignancy may be the result of genetic changes caused by mutagenic agents (eg. ionizing radiation). Peroxides, which are also capable of generating free radicals, have been shown experimentally to enhance tumour progression[2].

Diseases of the Head and Neck Resulting from Radiation: The thyroid gland has been shown to be very sensitive to the neoplastic effects of radiation[8,10,11], but radiation also affects other areas of the head and neck (Fig. 1) [6,8]. Parathyroid tumours (usually resulting in hyperpara-thyroidism), benign and malignant tumours of the parotid and submandibular glands, breast cancer, bone cancer, and oral squamous cell cancers have been described [12,13]. Squamous and basal cell carcinomas of the skin, as well as chronic radiation dermatitis (characterized by atrophy, telangiectasia, scarring, pigmentation and ulceration) have also been found (Fig.1) [9].

One study analyzing children who received radiation to the thymus gland (a common practice in the 1930's, 40's and 50's for infants with "thymic enlargement") demonstrated a dose-response relationship between radiation and thyroid cancer[10]. A linear relationship was observed over a range of 0.05 to 10.0 Gy. While most other studies have found a similar relationship[8], it is not clear whether the relationship remains linear at very low and at high doses. Another study also showed a convincing increase in the incidence of thyroid cancer as well as other tumours in individuals who had received radiation for childhood tinea capitis[11]. A recent study has found a 38.4% incidence of nodular thyroid disease in 2914 patients irradiated for benign conditions of the head and neck before their 16th birthday[8]. The majority received 7.5 to 9.0 Gy as treatment for enlarged tonsils.

A study of Marshall Islanders (a population with a high exposure to radiation as a result of nuclear bomb testing) has found a large proportion of children with nodular thyroid disease[14]. These studies have also found that the risk is greater for women and inversely related to age at exposure.

Management of Radiated Patients: The effects of radiation are delayed for many years, and many individuals are unaware that they were irradiated as children[8]. Therefore, there is frequently a lack of information about the precise radiation dose to the head and neck region. In estimating the dosage, it is helpful to delineate the site, the number of fractions, and the age at the time of exposure, if possible. Additional information regarding prior head and neck neoplasia and a family history is also important[8].

If a radiation history has been established, the patient should receive periodic examinations directed toward

detection of tumours associated with radiation[8]. A number of prophylactic options should be considered. If there is a normal thyroid examination, high frequency real-time, high-resolution ultrasonography should be considered[15,16]. The ultrasound is a more sensitive method of detecting thyroid nodules than physical examination. The ultrasound is also more sensitive and specific than the nuclear scan without the radiation exposure, but its effectiveness is highly operator-dependent[8,15,16]. If a small, nonpalpable nodule is detected, a fine needle aspiration biopsy should be performed. The patient should be examined annually, have repeat thyroid ultrasound at two-year intervals, and receive thyroid suppression therapy sufficient to result in an undetectable level of TSH. Thyroid hormone treatment has been shown to be effective both in tumour prophylaxis for irradiated patients who have remained free of disease and in prevention of recurrent cancer following thyroidectomy[8,17]. It is particularly recommended in cases of high radiation dose, high serum thyroglobulin, or a family history of thyroid carcinoma[8].

Surgery is usually indicated for patients with multiple thyroid nodules and a radiation history because of the 30-60% frequency of cancer, and radiogenic thyroid tumours are more frequently multicentric than nonradiogenic thyroid tumours[8,18]. If the fine needle aspiration biopsy is cellular or malignant, a near-total thyroidectomy appears to be the treatment of choice as lesions are frequently bilateral[8].

Protective Measures: Increased awareness of the potential dangers of ionizing radiation has brought about various protective measures. "Benign" conditions such as acne, facial hair, and enlarged thymus are no longer treated with radiation[6]. However, occupation and radiotherapy persist as potential sources of radiation exposure[19,20].

Currently, protective measures include the use of lead - a protective material - which is found in walls, glass barriers, aprons, and gloves in X-ray facilities[21]. Thyroid collars containing lead are used with dental X-rays. As well, the X-ray units are enclosed in X-ray-proof housing. Strict occupational safety controls are emphasized and, where contact with radiation is inevitable, film badge dose-meters are worn which provide a record of the individual dose received by each worker[19,21].

Case Examples of Radiation Tumorigenesis: During a summer student fellowship spent in the combined endocrine-neoplasia clinic at Mount Sinai Hospital, a number of patients were encountered who had previously been exposed to radiation and were referred for surgery to the head and neck region. Four cases illustrate the various clinical presentations and the importance of the problem.

Figure 1. Left: Received radiation for facial hair epilation 50 years before. Chronic radiation dermatitis and a skin graft on the chin (after resection of a basal cell carcinoma) are seen. Right: Front view shows scar in lower neck of recent parathyroidectomy.

The first two cases are examples of patients who received radiation treatment for benign conditions when its use for these purposes was acceptable. The third case involves occupational exposure to radiation. The final case illustrates a patient who received radiotherapy for cancer.

Case 1 (acne): A 48-year-old male who received radiation treatment to his face, shoulders and back for acne 30 years previously, presented with a firm 1 cm thyroid nodule. A nuclear scan indicated it was cold (non-functioning) and ultrasound showed it to be solid with patchy calcification. A pre-operative ionized calcium was 1.38 mmol/L (normal 1.17-1.33). At surgery, a multicentric papillary carcinoma of the thyroid and parathyroid adenoma were encountered and a near-total thyroidectomy and a parathyroidectomy were performed. He received further therapy with 80 millicuries (mCi) of radioactive iodine (I-131).

Case 2 (keloid): A 63-year-old female who had received radiotherapy for a presternal keloid 30 years previously, presented with a firm thyroid nodule. Thyroid function tests were normal except for a serum TSH of 3.7 mIU/L (normal 0.25-3.1). The scan showed a cold nodule and fine needle aspiration biopsy was cellular. A near total thyroidectomy revealed mixed papillary-follicular carcinoma. A lung tumour resected four years before and diagnosed as carcinoid was now re-evaluated as metastatic follicular thyroid carcinoma. A subsequent bilateral neck dissection revealed positive lymph nodes. She received two courses (80 and 120 mCi) of radioiodine.

Case 3 (occupational): A 38-year-old female dental hygienist, who had received multiple dental X-rays during her training in the mid-1970s, presented with primary hypercalcemia on a routine blood test (ionized calcium at 1.47 mmol/L and PTH at 8.6 pmol/L). Ultrasound was negative except for cervical lymphadenopathy. A parathyroidectomy was performed revealing adenoma. As well, multifocal lymphadenopathy and diffuse thyroid enlargement due to chronic thyroiditis were encountered. Subsequent thyroid function tests (TSH at 5.0 mIU/l) have indicated hypothyroidism, and she has been placed on longterm L-thyroxine therapy.

Case 4 (Hodgkin's disease): A 31-year-old female who received upper mantle radiotherapy for Hodgkin's disease five years ago, presented with a thyroid lump and numerous symptoms and signs of hyperthyroidism. A scan indicated a 2 cm cold nodule in the left lobe. A near-total thyroidectomy and left neck dissection were performed. Pathology revealed a malignant Hurthle cell tumour and diffuse thyroid hyperplasia. She has received 80 mCi of radioiodine. She is currently well without evidence of recurrent disease.

As the above examples demonstrate, radiation-associated head and neck disease is an ongoing problem. There are many individuals who were exposed to radiation when regulations against its use in benign conditions were lax. While radiation treatment for acne and other benign problems is no longer acceptable, occupational exposure and tumour treatment continue to be factors in assessment. Periodic examinations, thyroid hormone feeding, diagnostic imaging and surgery should all be considered in an effective treatment policy for patients with a history of exposure to radiation.

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References

1. Upton AC. Health effects of low-level ionising radiation: B iological basis for risk assessment. In: Health effects of low-dose ionising radiation. London, British Nuclear Energy Society, 1988: 3-13.

2. Bowden GT, Jaffe D, Andrews K. Biological and molecular aspects of radiation carcinogenesis. Radiation Research 1990;121:235-41.

3. Geard CR. Radiation-induced chromosomal changes and oncogenic transformation. In: Chadwick KH, Seymour C, Barnhart B, eds. Cell transformation and radiation-induced cancer. New York, Adam Hilger, 1990: 163-75.

4. Adams GE, Cox R, Humphreys ER. Biological effects of ionizing radiation: dose and dose-rate relationships. In: Health effects of low-dose ionising radiation. London, British Nuclear Energy Society, 1988: 19-23.

5. Borek C, Ong A. Molecular mechanisms in radiogenic transformation of rodent and human cells. In: Chadwick KH, Seymour C, Barnhart B, eds. Cell transformation and radiation-induced cancer. New York, Adam Hilger, 1990: 223-9.

6. Palmer JA, Mustard RA, Simpson WJ. Irradiation as an etiologic factor in tumours of the thyroid, parathyroid, and salivary glands. Can J Surg 1980; 23(1): 39-42.

7. Berry RJ. Pioneer to guinea-pig - the dawning of awareness of radiation risks. In: Health effects of low-dose ionizing radiation. London, British Nuclear Energy Society, 1988:17-8.

8. Schneider AB. Radiation-induced thyroid tumors. Endocrinology and Metabolism Clinics of North America 1990; 19(3): 495-508.

9. Rosen IB, Walfish PG. Sequelae of radiation facial epilation (North American Hiroshima Maiden syndrome). Surgery 1989;106(6): 946-50.

10. Hempelmann LH, Hall W, Phillips M, et al. Neoplasms in persons treated with X-rays in infancy. J Natl Cancer Inst 1975; 55: 519-30.

11. Ron E, Modan B, Preston D, et al. Thyroid neoplasia following low-dose radiation in childhood. Radiation Res 1989; 120:516-9.

12. Committee on the Biological Effects of Ionizing Radiations: Health Effects of Exposure to Low Levels of Ionizing Radiation. BEIR V. Washington, National Academy Press, 1990: 281-325.

13. Hildreth NG, Shore RE, Dvoretsky PM. The risk of breast cancer after irradiation of thymus in infancy. N Engl J Med 1989; 321: 1281-4.

14. Conard RA. Summary of thyroid findings in Marshallese 22 years after exposure to radioactive fallout. In: DeGroot LJ ed. Radiation-associated thyroid carcinoma. New York, Grune & Stratton, 1977: 241-57.

15. Hay ID. Thyroid nodules and thyroid cancer. Medicine North America 1990; 13:1669-79.

16. Riccabona G. Thyroid cancer. Berlin, Springer-Verlag, 1987:62-3.

17. Samaan NA, Schultz PN, Ordonez NG, et al. A comparison of thyroid carcinoma in those who have and have not had head and neck irradiation in childhood. J Clin Endocrinol Metab 1987;64(2): 219-23.

18. Robbins J. Thyroid suppression therapy for prevention of thyroid tumors after radiation exposure. In: DeGroot LJ ed. Radiation-associated thyroid carcinoma. New York, Grune & Stratton, 1977: 241-57.

19. Ball JL, Moore AD. Essential physics for the radiographer. London, Blackwell, 1980: 217-25.

20. Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. N Engl J Med 1991; 325:599-605.

21. Sinclair WK. Radiation protection policy: implications for the future. In: Sinclair WK ed. Radiation Protection Today. Bethesda, NCRP, 1989: 343-55.

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The Therapeutic Use of Laughter in Pediatric Patients

Sheryl Nirenberg, 9T2

Abstract

It is important for health care professionals to understand the normal development of laughter from infancy to adulthood in order to utilize this potentially powerful therapeutic tool. The use of laughter as a form of therapy is discussed in this paper as well as its potential abuse. Laughter can have an effect on mood, stress, anxiety and pain and can be used to teach children about their disease.

Introduction

"Laughter is the best medicine", is a common aphorism which has become clinically significant. Laughter and humor have been suggested as valuable adjuncts to medical treatment.[1] Norman Cousins, who suffered from ankylosing spondylitis, used positive emotion, primarily laughter, to relieve the symptoms of his illness. He found that laughter had both an anesthetic effect and allowed pain-free sleep.[1] While laughter has been cited as a therapeutic modality with adults, very little is known about the use of laughter in the pediatric population. This paper will examine the potential use of laughter as a therapeutic agent for sick children.

Historically, humor referred to a balance of the four basic bodily fluids: choler, melancholy, blood and phlegm.[2] A person was said to be in good humor when the four fluids were in proper equilibrium. Aristotle believed that laughter was a means of correcting the imbalance of these four humors. Today, humor refers to those attributes of an event which result in laughter.[2]

Humor is an abstract concept and not an emotion, although it may function as a stimulus for changing one's emotional state. It usually involves the mental task of recognizing an incongruous situation and receiving some pleasure at the time of its resolution.[2] Laughter is defined as a "series of spasmodic and partly involuntary expirations with inarticulate vocalization...".[3, 4] Physicians, health-care workers and parents should be aware of the normal developmental patterns of laughter in children so they can maximize its potential for enhancing well-being.

Development

Smiling is a biological phenomenon first seen during the neonatal period. It occurs in response to pleasant external stimuli such as human faces or voices.[3,5] It is at eight weeks of age that a baby's smile becomes more selective, occurring in response to familiar people.[6] Congenitally blind infants begin to smile at the same age as sighted infants[7,8] suggesting that their channels of recognition are also sensory. Although a sighted infant at two months of age will smile in response to a human face, the blind child will not.[9] Auditory stimuli will evoke a smile in a blind two-month-old baby and the most effective stimulus for a smile from a blind child is the primary caregiver's voice.[9] Although blind infants smile less frequently than their sighted counterparts, it is important parents of blind children not misinterpret the lack of smiling as signifying an unhappy or unresponsive child.

Smiles occur in response to mildly novel and intriguing stimuli.[5] The child interprets these stimuli within the context of the familiar environment. If a stimulus has some familiar properties, then it will elicit a smile. The amount of effort expended to appreciate any new image must not be insurmountable. A completely unknown stimulus requires too much effort to understand (i.e. fit into the cognitive scheme) and instead of eliciting a smile, it will cause fear. Repeated presentations of a familiar stimulus will produce a smile as long as it continues to have arousal properties. Familiarity will cause boredom and the stimulus will no longer produce a smile.

Laughter first appears at four months of age in response to tickling.[5] At eight months of age, laughter can be induced by a game of 'peek-a-boo'.[5] Babies laugh out of pleasure, not because they understand the cognitive elements of the interaction.[10] At one year of age, the child will laugh in response to an absurd event which may suggest a basis for understanding the intellectual side of humor.[2,5] A child's make-believe world is an incongruous situation where imaginary objects are used in place of real objects. The resolution of an initially illogical or inconsistent event at the child's own level of understanding results in laughter.

Nursery school children laugh when they have completed a challenging task or when they anticipate this accomplishment.[3] Children laugh more often when in social situations than when they are alone.[3] A child will laugh at a younger child with less developed abilities[5]—for example, the incorrect usage of language by one child will induce laughter in a child who has already mastered language rules. At six years of age, the child begins to understand verbal humor in the form of an anecdotal joke and will develop a repertoire of age appropriate jokes.[11] From eight to ten years of age, children will create their own humor through puns and practical jokes. The child may also take pleasure and laugh at the misfortune of others.[11]

Ten to fourteen-year-olds will exhibit a more aggressive slapstick humor as they 'clown around' and throw insults at one another.[11] School girls may have hysterical fits of laughter.[12] The adolescent has a more developed abstract level of cognitive understanding and catches the subtle meaning behind jokes. The more intelligent adolescent can understand the complex social relationships in humor and subsequently laughs more often.

Adolescents may laugh to disguise ignorance. In a social situation where the adolescent does not understand a joke, but realizes that one has been told, he or she may laugh along with the others in order to maintain group acceptance.[13] Adolescents may laugh to hide embarrassment, shyness or a particular thought.[14] Similarly, they may laugh in response to trivial stimuli in order to be congenial and likeable. This laughter is initiated voluntarily and is not a true expression of emotion.[14]

In comparison to adults, children have less complex cognitive abilities and subsequently are not able to resolve the incongruity underlying complex jokes.[15] In many instances, children have not formed the biases that many adults have and therefore do not understand jokes directed against religious or ethnic groups.[16] Children do not appreciate sexual jokes, a form of humor which may aid in developing a bond between two people.

Children laugh at different stimuli than do adults. This may explain why adults sometimes do not understand what is funny to a child.[5] Similarly, children do not understand what adults find humorous. Naive comments from a child may be amusing to an adult, although the child will not understand why this is so.

Social Factors and Laughter

Some people may be predisposed by factors in their environment to be able to laugh and to appreciate humor. Humor development in a child can be predicted best by a child's behaviour from the age of three. Children three to five years of age who have had a protective and loving relationship with their parents (especially mother) were found later in life to have an enhanced appreciation of humor. Children six to eleven years of age with an enriched sense of humor tended to have parents who were not protective (females only) and who allowed them opportunities to solve problems on their own (both sexes).[17] Early independence may have produced anxiety in these children and may be related positively to humor development. Physical and verbal assertiveness was

correlated with humor development in both sexes.

Children's use of humor and their school performance may give some insight into their home life. As young children, professional comedians were found to have been given large amounts of responsibility. They cared for siblings, lent support to their parents, and earned money while very young. Their mothers never formed a close bond with them and the mothers did not have innate maternal instincts. Consequently, as children, comedians could only receive parental acceptance by living up to unreasonably high expectations.[18] These children used humor to cope with their less than adequate home situations.[5]

Therapeutic Applications of Laughter

During illness, pediatric patients have many stresses which are not always disease related. Hospitalized children are separated from their family, often for the first time. The hospital is an intimidating environment where children are surrounded by many strangers, including health-care professionals, visitors and other patients. Long hospitalizations may act as chronic stressors and disturb the development and maintenance of previously achieved milestones. Normal sleep patterns may be disrupted by the unfamiliar environment and/or as a result of medical treatment. Furthermore, children may not adapt to hospital dietary changes.

The stress of an illness may be relieved by laughter. Scientists have found improved function of the immune system following the viewing of a humorous film.[19,20] In association with the viewing of the film, concentrations of secretory immunoglobulin A (sIgA) were enhanced for several minutes after the film.[19,20] Immunoglobulin, present in saliva, intestinal secretions and tears, normally functions in the defence against viruses and bacteria on mucosal surfaces. Although the longterm effect of this brief elevation in immunoglobulin has not been determined, a lasting sense of humor may have lasting health benefits.[19,20] Humorous film clips tend to reduce stress especially in those individuals who most often rely on humor to cope with anxiety.[20]

There is documentation the immune system may be depressed after a stressful event.[19] Life events which cause an increased sense of inner tension tend to raise epinephrine levels and lower the sIgA level.[19] Fry and Rader[13] suggested that the increase in epinephrine stimulated endorphin production which in turn alleviated immune depression.

Other researchers believe laughter improves immune function by reducing epinephrine and cortisone levels which normally act in immunosuppression.[20] Possibly, by perceiving some humor in a situation, the individual will not feel threatened by such a situation and there will be no sympathetic adrenal response.[21] Alternatively, individuals who have stressful life events may counteract their feelings of anxiety by appreciating the humorous aspects of their lives.[21]

Laughter decreases stress, relieves anxiety and depression, improves the quality of life in the ill and adds a more humanistic approach to medicine.[11] Empathic responses and patient motivation can be achieved with humor.[11,22] Laughter has effects similar to physical exercise[6] and can stimulate a patient's appetite.[23] This may be of particular benefit for pediatric patients whose appetites have been altered by their hospital stay.

Laughter raises discomfort thresholds.[24] Cogan, et al[24] claim physical discomfort decreased in subjects who had listened to a laughter-inducing tape. Patients undergoing medical treatment associated with short-term pain (e.g. injections or postsurgical pain during recovery) may benefit from laughter-inducing strategies.[24] Laughter prior to surgery decreased fear, anxiety and anger and patients did better postoperatively.[25] In addition, some authors suggest laughter can be utilized to aid post-operative patients in learning to cough and breathe deeply,[12,26] thus reducing the risk of respiratory complications.

Pediatric oncology patients benefit from laughter and humor.[6] Laughter allows children to cope better with long hospitalizations. Humor may be used in the teaching process and may reduce fear and anxiety associated with chronic illness. Humor allows people to ask questions they may be too embarrassed, shy or anxious to ask thereby initiating the education process so crucial for the ill child. Laughter may help pediatric patients in accepting their changed bodies and lifestyles. The physician may also employ gentle humor with the family members who find it difficult to accept the frightening situation of an unhealthy child.[11]

Appropriate Use of Humor

Humor and laughter have therapeutic applications in the health care setting.[11,16,22,26] Their use, however, carries a warning as the timing, content and receptiveness to the humorous stimuli should be monitored.[6,22] Humor should be avoided during an acute crisis, but may be helpful after the crisis to decrease tension. Also, humor should never be directed against someone and one should laugh with the patient not at the patient. Sarcastic, ethnic, cultural or sexually suggestive jokes are never appropriate. The type of humor used by the patient gives the physician some knowledge of unexpressed emotions.[27] Humor which is attacking or hostile indicates anger which requires further investigation. A patient who will

humor or who is unable to see the humor in a situation may be experiencing chronic stress.[27] The use of humor after a long absence may indicate the patient is beginning to recover[22] and so, humor can be used to monitor the patient's emotional state.[27]

Conclusion

The use of humor is one method through which children and family members actively participate in the child's recovery. It is a method of self-medication which has not yet been fully explored and utilized. Humorous stimuli vary with the age of the patient and should be considered by the physician when choosing appropriate laughter-inducing modalities. The stimulus which provides the best therapeutic value for specific ages and the effect of individual differences is unknown. More research specific to pediatric humor is required to maximize the therapeutic value of laughter in children.

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References

1. Cousins N. Anatomy of an Illness (as perceived by the patient). N Engl J Med 1976;295:1458-1463

2. McGhee PE. Humor: Its Origin and Development, San Francisco, W. H. Freeman and Company, 1979

3. Stearns FR. Laughing, Springfield, Charles C. Thomas, 1972

4. Dorland's Medical Dictionary, ed 27. Philadelphia, WB Saunders Co., 1988,p.899

5. Ziv A. Personality and Sense of Humor, New York, Springer Publishing, 1984

6. Bellert JL. Humor: A therapeutic approach in oncology nursing. Cancer Nurs 1989;12:65-70

7. Emde RN, Harmon RJ. Endogenous and Exogenous Smiling Systems in Early Infancy. J Am A Chil 1972;11:177-200

8. Gleitman H. Psychology, (ed.2) New York, WW Norton & Co., 1986

9. Warren DH. Blindness and Early Childhood Development, (ed.2) New York, American Foundation for the Blind, 1984

10. Holland NN. Laughing: A Psychology of Humor, Ithaca, Cornell University Press, 1982

11. Robinson VM. Humor and The Health Professions, New Jersey, Charles B. Slack, 1977

12. Askenasy JJM. The Functions and Dysfunction of Laughter. J Gen Psychol 1987;114:317-334

13. Foot HC, Chapman AJ. The Social Responsiveness of Young Children in Humorous Situations. In: Chapman AJ, Fort HC (eds.). Humour and Laughter: Theory, Research and Applications, London, John Wiley & Sons, 1976,pp.187-214

14. Young PT. Emotion in Man and Animal, (ed.2) New York, Robert E. Krieger Publishing Co., 1973

15. Shultz TR. A Cognitive-Developmental Analysis of Humour. In: Chapman AJ, Foot HC (eds.). Humour and Laughter: Theory, Research and Applications, London, John Wiley & Sons, 1976,pp.11-36

16. Haig R. Some Sociocultural Aspects of Humour. Aust N Z J Psychiatry 1988;22:418-422

17. McGhee PE. Humor Development: Toward a Life Span Approach. In: McGhee PE, Goldstein JH (eds.). Handbook of Humor Research Vol I, New York, Springer-Verlag, 1983,pp.109-134

18. Fisher S, Fisher RL. Personality and Psychopathology in the Comic. In: McGhee PE, Goldstein JH (eds.). Handbook of Humor Research Vol II, New York, Springer-Verlag, 1983,pp.41-59

19. Saper B. Humor in Psychiatric Healing. Psychiatr Q 1988;59:306-319

20. Long P. Laugh and Be Well? Psychol Today 1987;Oct:28-29

21. Martin RA, Dobbin JP. Sense of Humor, Hassles, and Immunoglobulin A: Evidence for a Stress-Moderating Effect of Humor, Int J Psy M 1988;18:93-105

22. Leiber DB. Laughter and Humor in Critical Care. Dimensions of Critical Care Nursing 1986;5:162-170

23. Ellis S. Humor: The Wonder Drug. Nurs Times 1978; Nov:1792-1793

24. Cogan R, Cogan D, Waltz W, McCue M. Effects of Laughter and Relaxation on Discomfort Thresholds. J Behav Med 1987;10:139-144

25. Schiffer RB, Herndon RM, Rudick RA. Treatment of Pathologic Laughing and Weeping with Amitriptyline. N Engl J Med 1985;312:1480-1482

26. Simon JM. Therapeutic Humor: Who's Fooling Who? J Psychosoc Nurs 1988;26:8-12

27. Sumners AD. Humor: Coping in Recovery from Addiction. Issues Ment Health Nurs 1988;9:169-179

Paediatric Presentations

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Give a diagnosis and treatment plan for each of the following cases:

Case 1

Two days prior to admission, this previously healthy three-year-old boy was noted to have a puffy face by his mother. At that time, he was taken to his family doctor who noted mild periorbital and sacral edema. He was referred to you for further evaluation. Physical examination revealed an unhappy child with marked generalized edema. Heart rate was 110/min, BP was 90/70, and his weight was 16 kg. The rest of the exam was unremarkable.

Laboratory investigations revealed:

Urine		**Blood**
Specific Gravity	1.013	Urea 3.9 mmol/L
Protein	3.0 g/L	Creatinine 44 umol/L
Blood	negative	Albumin 22 g/L
Micro	Normal	Hemoglobin 125 g/L
		WBC 12.5 x 10^9/L
		Serum C3 complement normal
24 Hour Urine		
Creatinine clearance		1.9 mL/s 1.73 m^2
Protein		3.5 g

Answer to Case 1: This is a classic presentation of Nephrotic Syndrome (NS) which is characterized by severe proteinuria (>50 mg/kg/d), hypoalbuminemia (serum albumin <25 g/L), edema and hyperlipidemia. The most common cause of NS in this age group is Minimal Change Nephrotic Syndrome (76% of all NS cases). The goal of treatment is the reduction in the excretion of urinary protein by the use of corticosteroids such as prednisone at a dose of 2 mg/kg/d. If the proteinuria does not remit within 28 days of daily adequate steroid treatment, this is an indication for re-evaluation or change in therapy.

If the diagnosis was made on the basis of clinical and laboratory features alone, a renal biopsy is indicated when there is resistance to steroid therapy, frequent exacerbations in the patient's condition, hematuria, or renal failure. Biopsy is also used to establish the precise diagnosis of other renal diseases such as Focal Segmental Glomerular Sclerosis and Membranous Nephropathy which may also cause NS in children.

Case 2

This neonate was born early this morning at the Ajax-Pickering Hospital by C-section. The Apgar scores were recorded as 3^1 and 5^5. On examination, the baby was cyanotic, tachypnic with nasal flaring, and showed intercostal retraction with a scaphoid abdomen. On palpation, the trachea was found to be deviated to the right and on auscultation breath sounds were found to be absent over the left lung field. Bowel sounds, however, were noted in this region.

Answer to Case 2: This is a neonatal emergency. The infant is in respiratory distress and requires immediate NG tube insertion, intubation and ventilation. Upon stabilization, transfer the patient to a tertiary care centre ASAP.

This child has a Congenital Diaphragmatic Hernia (CDH). CDH is usually caused by a left-sided defect in the posterolateral aspect of the diaphragm which allows abdominal contents to herniate into the thorax. Clinical diagnosis is confirmed by a chest X-ray. On the X-ray, note the presence of loops of bowel in the left thorax as well as the shift of both the mediastinum and the trachea to the right.

The initial treatment is to address the respiratory distress. The NG tube was inserted to decompress the stomach and small intestine thereby allowing the hypoplastic lungs to inflate. The child was intubated and ventilated to alleviate his respiratory distress and to correct the respiratory acidosis. Once the baby is stable, surgery is performed to repair the hernia. Unfortunately, the baby may have long-term respiratory problems as a result of his hypoplastic lungs (ie. abnormal lung development due to compression in utero).

Case 3

This six-year-old boy presented with complaints of pain in his knees and ankles, abdominal discomfort and spots on both lower legs. The history revealed that the child had a cold one week ago and that the abdominal pain had manifested acutely and felt crampy. On examination, the affected joints were found to be swollen and tender on movement. Circular purpuric lesions were present on the lower extremities.

Answer to Case 3: In cases such as this, when the patient presents with multiple system involvement, diagnostic confusion may result when one system predominates. For example, the rash may suggest a hemorrhagic diathesis or

septicemia. A platelet count, blood clotting tests and culture will help exclude these possibilities. When GI manifestations predominate, this may suggest a number of intra-abdominal emergencies. Still, the possibility of Henoch-Schonlein Vasculitis (HSV) should be considered in any child with a rash, acute abdominal pain and arthritis. One should also inquire about any possible renal involvement. Another difficulty in diagnosing HSV, is that laboratory investigations are generally non-specific. Thus, the diagnosis is normally based solely on the interpretation of its clinical manifestations. Classically, the onset of HSV follows a nonspecific upper respiratory tract infection as in this case and this fact, once again, emphasizes the importance of a good history.

In most cases, treatment for HSV is symptomatic because in 90% of patients, the disease is self-limiting. However, the short-term use of corticosteroids may be indicated for severe GI pain or bleeding. Steroid therapy for the nephritis that often accompanies HSV is presently still controversial. The long-term prognosis is dependent on the degree of renal disease with 5% of patients with renal involvement developing chronic renal failure and eventually requiring renal transplantation.

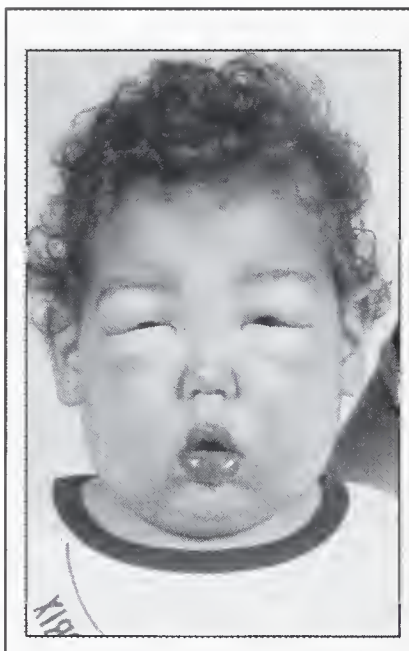

Figure 1: Case 1a

Figure 2: Case 1b

Figure 3: Case 2

Figure 4: Case 3

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The 1991 Gairdner Foundation International Awards

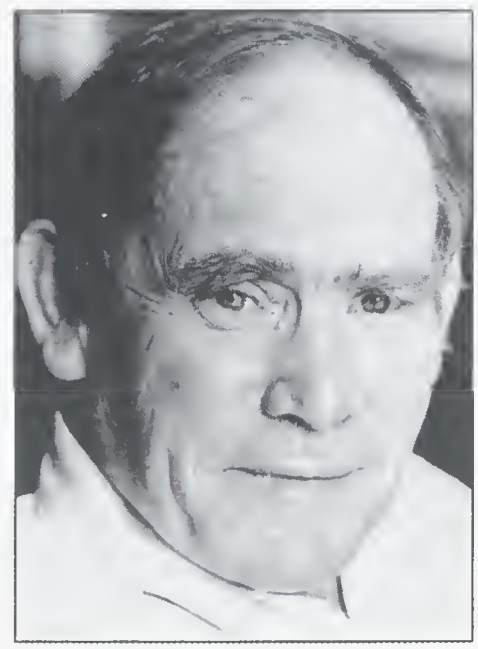
On Friday October 25, 1991, six scientists received the 1991 Gairdner Foundation International Awards for outstanding contributions in the field of medical science. The winners were selected by the Foundation's Medical Advisory Board which was chaired by Dr. Charles Hollenberg, the president of the Foundation, and they included one researcher from Canada, two from England, and three from the United States.

In the past, the Foundation has honoured 218 scientists with awards of $30,000 to help further their research and 37 of those honoured have subsequently received a Nobel Prize. This year, the awards were presented by Professor Geraldine A. Kennedy-Wallace, the president and vice-chancellor of McMaster University.

The two British winners from the University of Cambridge, Dr. Sydney Brenner from the MRC Molecular Genetics Unit and Dr. John E. Sulston of the MRC Laboratory of Molecular Biology, were recognized for their establishment of a model system for following the process of the development of a single fertilized egg into a multi-celled organism. In order to accomplish this feat, these men chose to study Caenorhabditis elegans, a one millimetre-long nematode which lives in the soil and has the remarkable property of having exactly 959 cells.

John E. Sulston

By studying C. elegans, Dr. Sulston has become the only person to have observed and described the complete development of an animal at the cellular level. He carefully recorded every cell division of C. elegans and subsequently developed a lineage map indicating the genealogy of each of its 959 cells as well as their ultimate destiny in the various organ systems of the adult. Dr. Sulston then went on to characterize specific genetic alterations and their effects on the normal development of C. elegans.



Sydney Brenner

Dr. Brenner, a previous winner of the Gairdner Award in 1978 for his contributions in the fields of molecular biology and genetics, has also spent a great deal of time studying C. elegans. In 1974 he published the first detailed account of the genetics of C. elegans. He chose this tiny nematode because its relative anatomical and genetic simplicity facilitated a complete description of its development.

Together, Drs. Brenner and Sulston described the cell-by-cell development firstly of the roundworm's nervous system and then of the entire animal, an unparalleled feat in biology. Currently, they are part of a major effort to clone and sequence the entire C. elegans genome which will hopefully give scientists an intimate understanding of the role genes play in development, behaviour, and carcinogenesis.

The American winners included Dr. M. Judah Folkman of the Harvard Medical School who was cited for his contributions to the understanding of angiogenesis. Dr. Folkman was one of the pioneers in studying gas and drug transport across semi-permeable membranes and his early work played a major role in the field of implantable, sustained drug-releasing devices. More importantly, he

M. Judah Folkman

was one of the first to identify factors that promoted angiogenesis.

Indeed, he has isolated these regulatory angiogenic factors, helped develop bioassays for them and studied the angiogenic effects of heparin, protamine, and steroid hormones. He also showed that cancer cells produce substances that cause localized angiogenesis in order to provide the increased blood supply needed by the growing cancerous tissue. This work is continuing to play a major role in the ongoing understanding of tumour development, growth, invasion, and metastasis. Presently, Dr. Folkman is studying the possible role of angiogenesis in the evolution of peptic ulcer disease and his contributions in both of these areas may have important long-term therapeutic implications.

Robert F. Furchgott

In a totally different vein, Dr. Robert F. Furchgott at the State University of New York Health Centre at Brooklyn discovered that endothelial cells lining blood vessels released a substance now called endothelial-derived relaxing factor (EDRF). In 1980, he showed that EDRF acts as a messenger to modify the function of smooth muscle cells in these blood vessels which in turn affects both their diameter and the blood flow through them. It was subsequently found that EDRF was actually nitric oxide, and that it had the same pharmacologic actions as exogenously administered nitrate vasodilators.

In addition, EDRF was also shown to affect platelet aggregation in arteries. Thus, damage to endothelial cells, whether by atherosclerosis or experimentally-induced trauma, may result in a decrease in EDRF production which would then lead to arteries that fail to relax as well as increased platelet aggregation. Dr. Furchgott's findings have stimulated research worldwide in the physiology and pathophysiology of blood vessels, and have had a major impact on our understanding of all vascular disease and particularly atherosclerosis-induced organ ischaemia.

The third American researcher, Dr. Kary B. Mullis from the Nucleic Acid Chemistry Company, La Jolla, California, was acknowledged for his discovery of the polymerase chain reaction (PCR). The importance of this development was shown when the enzyme which makes PCR possible, DNA polymerase, was designated Molecule of the Year by the journal Science in December. The technique allows for an almost unlimited amplification of nucleic acid sequences.

To accomplish this feat, PCR depends on the availability of a heat-stable DNA polymerase which originally extracted from the bacterium Thermus aquaticus as well as specific primer oligonucleotides. These primers allow for the targeting of specific DNA sequences which are then repeatedly replicated by the polymerase. This technology has revolutionized molecular genetics by allowing genes to be readily isolated and amplified. This option is far superior to traditional cloning methods which were laborious and fraught with error.

PCR has already been used to assist in the study of genetic disease caused by human DNA mutations. It has also helped clone gene families that are highly conserved among a wide variety of organisms and has been used in criminology to characterize human DNA from small amounts of blood, semen, saliva, and even strands of hair. This DNA pattern is a better individual blueprint than fingerprints and has already been used in some legal cases to aid in the identification of offenders.

Finally, PCR is of paramount importance for the insertion of site-specific gene mutations in genetic engineering and has even been used to study genetic characteristics and relationships of long dead organisms in both archaeology and evolutionary biology. In the future, PCR's importance will probably continue to increase since it will help map the human genome and has provided scientists with a powerful new tool for genetic research.

To complete this list of distinguished scientists, Dr. David H. MacLennan from the University of Toronto was honoured for his work in the chemistry of muscle contraction for which he is world-renowned. Muscle contraction and relaxation is governed by intracellular calcium concentration with calcium ions are stored in the sarcoplasmic reticulum (SR) between contractions. In order to understand how calcium is pumped into the SR, stored there, and then later released, researchers first had to isolate and study the specific molecules involved.

Dr. MacLennan was the first person to successfully isolate virtually every major functional SR protein. In 1970, he identified the calcium ATPase pump. A few years later, he found a protein he called calsequestrin which binds calcium during the storage phase. In the 1980s by using the newly discovered techniques of gene cloning , he isolated the genes that encoded several muscle proteins including calcium ATPase. He then sequenced this gene and predicted the protein's three-dimensional structure.

Finally, he went on to develop a detailed model of the ATPase molecule and its function by altering specific base pairs of the gene and studying the effects on protein function. Recently, his laboratory has succeeded in cloning and sequencing the gene encoding the protein that forms the calcium releasing channels of the SR and Dr. MacLennan has postulated that it is a defect in this gene that gives rise to malignant hyperthermia.

The Gairdner Foundation International Awards were established in 1957 by the late James Arthur Gairdner. He was born in 1893 in Toronto and was both a scholar and a distinguished athlete. After serving the Canadian army in World War I, he then began a successful career in investment but at the age of 56, he suffered a severe attack of arthritis and decided to take up painting. In fact, many of his paintings presently are displayed in Gairloch Gardens, the place where he lived and painted in Oakville, Ontario, which has been converted into an art gallery.

Throughout his life, James A. Gairdner was interested in both clinical medicine and medical research and he strongly believed that there should be tangible recognition for the achievements of medical scientists.

Kary B. Mullis

With the encouragement of his close friend Dr. Wallace Graham, a leading Toronto rheumatologist, he established the awards, which have honoured scientists from 12 countries in the past 35 years. Initially, the awards were for achievements in the fields of arthritis, rheumatism, and heart disease but more recently, the awards have encompassed broad areas of medicine including immunology, genetics, and molecular biology. James A. Gairdner died in 1971, but his vision and legacy live on.

We are thankful to the Gairdner Foundation and the University of Toronto Department of Public Affairs for much of the above information.

David H. MacLennan

Instructions to Authors 1992-93

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A cover letter signed by all authors should state that the manuscript is not under consideration nor has been published by any other journal and explain the purpose of the paper and its intended readership.

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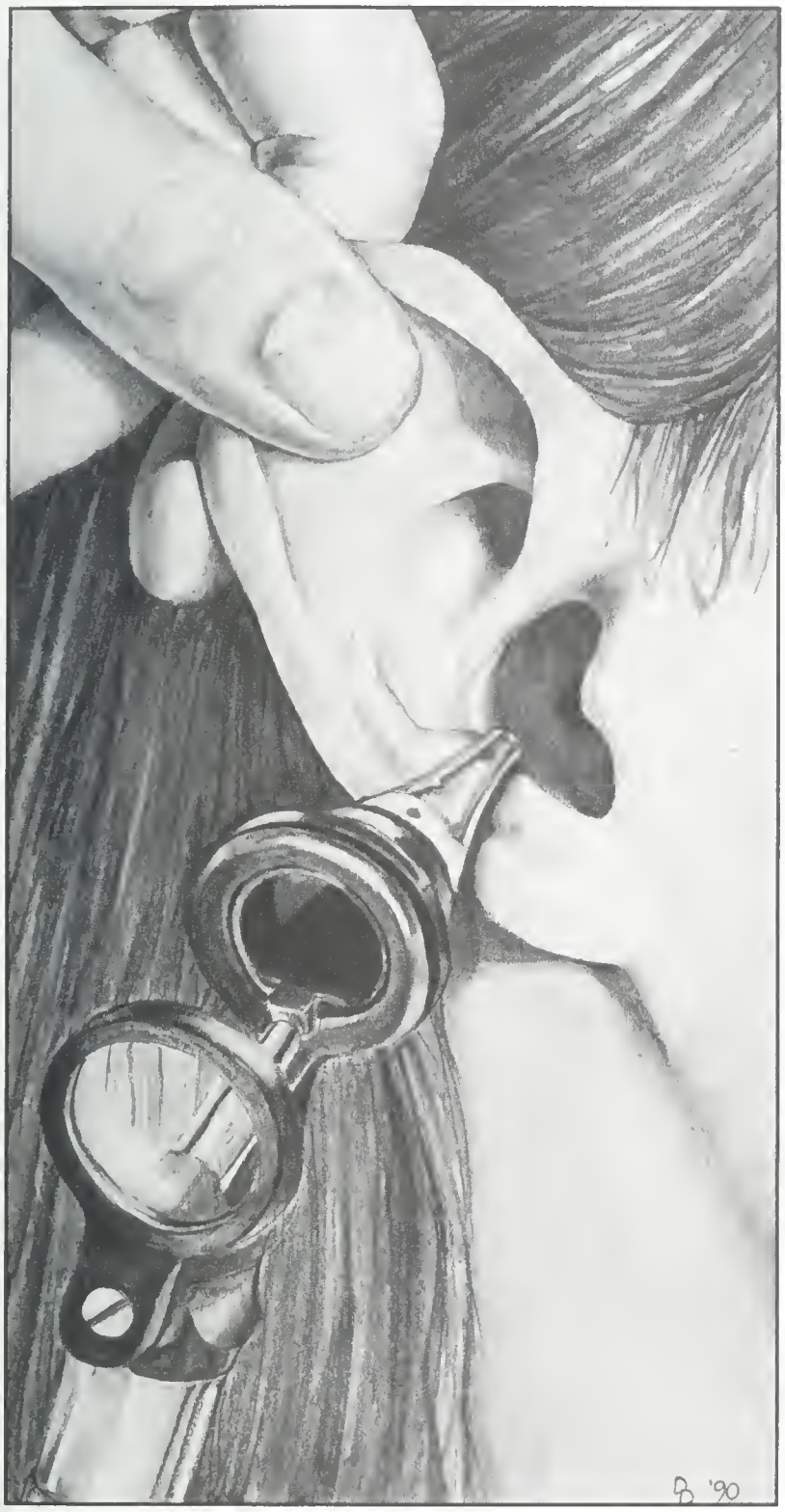

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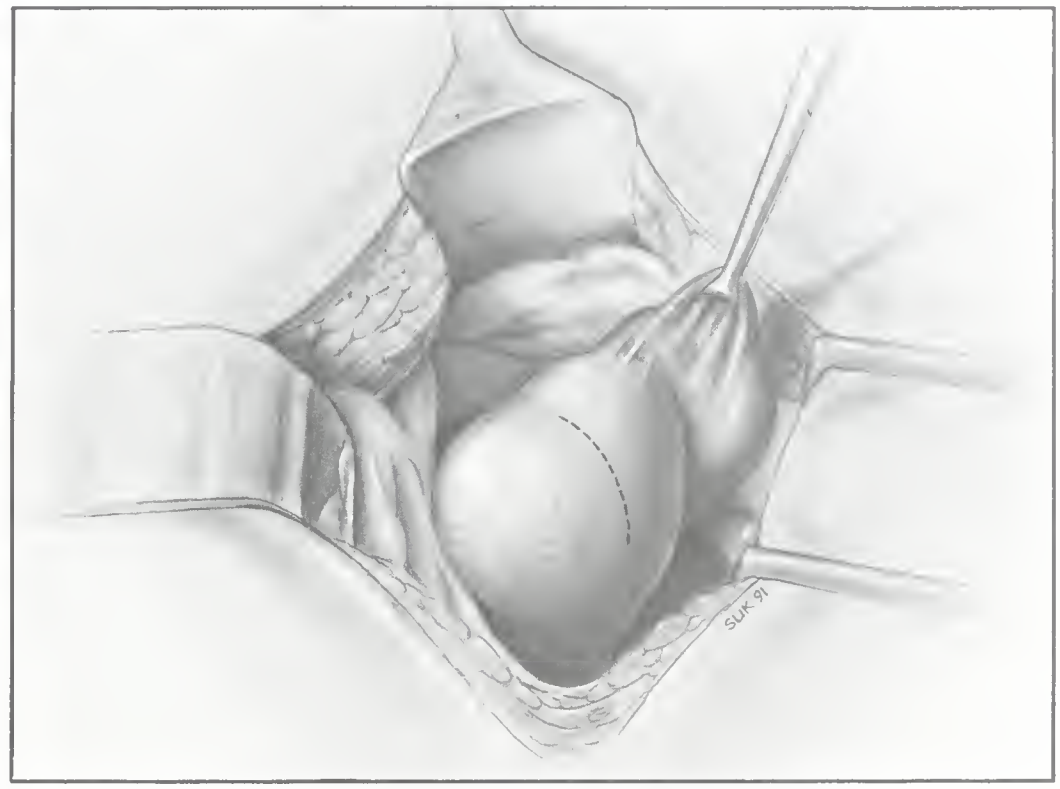

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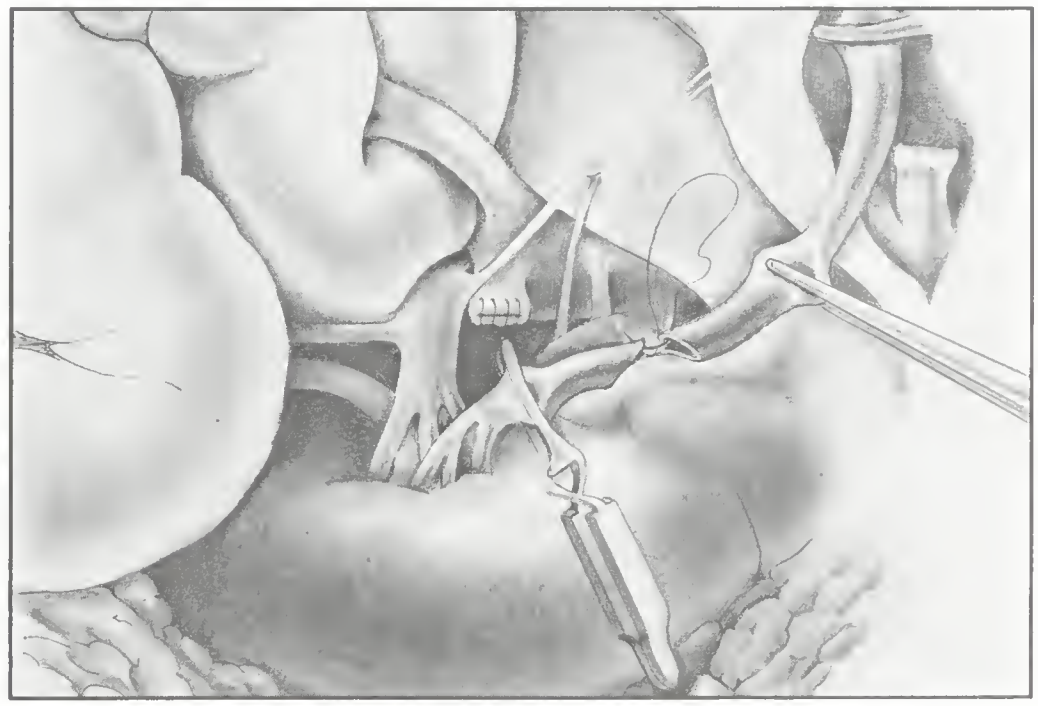

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